Develop New or Improved Approaches for Treating Disease and Disability

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New Medication, Nalmefene, Provides Another Option for Alcoholism Treatment

Background: One of the challenges researchers face in developing effective medications to treat alcoholism is that the exact molecular sites at which alcohol binds to cells remain unknown. Also under intensive study are the biological pathwaysBthat is, the predictable series of molecular reactionsBthat are triggered inside the cell once alcohol molecules have bound to it. Ideally, medications are designed to target the binding sites or the pathways that result in diseases, such as alcoholism.

While the search for optimal drugs for alcoholism treatment continues, scientists have developed some medications that have shown better than moderate success at preventing recovering alcoholics from relapsing. Key among these medications has been naltrexone, a drug recently approved by the Food and Drug Administration. Naltrexone is an opioid antagonist; that is, it works by blocking the component of the nervous system involved in processing substances that have opiate effects, such as alcohol.

Researchers recently completed a clinical trial of a new opioid antagonist called Analmefene.@ In previous studies in which naltrexone and nalmefene were compared, nalmefene resulted in lower risk of liver toxicity and entered the bloodstream more quickly. Nalmefene=s effects lasted longer than those of naltrexone, and data suggest that it may be more potent than naltrexone.

Advance: In this clinical trial, nalmefene significantly reduced relapse to heavy drinking among recovering alcoholics. Patients taking placebos were 2.4 times as likely to relapse as were patients taking nalmefene. None of the 105 patients who took part in the clinical trial suffered major adverse effects from nalmefene.

Implications: Nalmefene appears to be as effective as naltrexone and at least as safe. If this medication receives approval from the Food and Drug Administration (FDA), it will offer a new treatment option for alcoholics who are unable to take naltrexone. For example, nalmefene appears to be less toxic to the liver than is naltrexone, a significant issue for the many alcoholics who suffer from alcohol-induced liver disease. For these patients and for those who are allergic to naltrexone or for whom the drug is not effective, nalmefene may offer a valuable alternative.

Alcoholism affects 14 million adult Americans and costs the nation $166 billion each year. Scientists are making important discoveries regarding molecular sites at which alcohol binds to cells and the pathways by which alcohol alters cell function. These discoveries will contribute to design of more precisely targeted drugs for alcoholism treatment. While the search continues, patients now appear to have an improved medication option for the prevention of relapse.

This study has provided the basis for industry (a Finnish company) to plan further studies of nalmefene in heavy drinkers, with the intent of obtaining FDA approval.

Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB: A Double-Blind, Placebo-Controlled Study of Oral Nalmefene for Alcohol Dependence. Archives of General Psychiatry, 56:719-724, 1999.

Antibiotic Restores Critical Protein Production in Muscular Dystrophy Mouse Model

Background: Duchenne muscular dystrophy (DMD) is one of a group of genetic muscular dystrophies characterized by progressive weakness and degeneration of the skeletal or voluntary muscles that control movement. Nearly one-third of cases come from new mutations of the gene for dystrophin, which is unusually large and especially susceptible to mutations.

A particular class of antibacterial antibiotics called aminoglycosides have the ability to suppress certain gene sequences, called Astop codons,@ that inhibit protein production. Scientists tested a specific aminoglycoside, gentamicin, on cultured muscle cells from the *mdx* mouseBan animal model for DMD that has a stop codon in the gene for dystrophin. The resulting restoration of dystrophin in cultured cells encouraged the researchers to try the antibiotic on the mice themselves.

Advance: NIH-funded scientists (co-funded by the Muscular Dystrophy Association) have successfully applied the common antibiotic gentamicin to restore the function of the protein dystrophin in mouse models of (DMD). It is the absence of dystrophin which is responsible for this genetic muscle-wasting disease that affects 1 in 3,500 boys. The result of this study was that dystrophin was restored to the cell membranes of all the striated mouse muscles they examined. Furthermore, the treatment afforded the muscles protection against injury.

Implications: The discovery, say the scientists, may pave the way for a treatment in some human patients with DMD. The potential advantage of aminoglycosides for human DMD therapy may lie partly in the method of delivery. Gene therapy, the focus of much current interest for genetic disease treatment, works by using a Avector@Bfrequently a virusBto carry corrected genes to sites that will effect therapeutic change. Vectors, however, do not always hit their mark. By injecting an antibiotic, physicians could conceivably deliver the treatment more directly, simply, and systemicallyBa significant advantage in a disease affecting all the muscles in the body.

Barton-Davis ER, Cordier L, Shoturma DI, Leland SE, Sweeney HL. Aminoglycoside antibiotics restore dystrophin function to skeletal muscles of *mdx* mice. *Journal of Clinical Investigation* 1999;104(4):1-7.

Advances in Systemic Lupus Erythematosus B
Treating Mouse Systemic Lupus Kidney Disease with Short Protein Fragments

Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease primarily affecting women of childbearing age. Many organs can be involved and include skin, joint, heart, lungs, nervous system, and kidneys. Symptoms wax and wane, and range in severity from mild to life-threatening. Antibodies that recognize various aspects of the cellular machinery are found in patients with SLE. Such autoantibodies are markers of SLE and may be involved in causing specific organ damage. Therapeutic interventions in SLE are generally directed toward nonspecific immune suppression and are associated with significant morbidity and toxicity.

Advance: Mice treated with short peptides (protein fragments) derived from nucleosomes (a component of cells and a common target for SLE autoantibodies) prior to the development of signs of SLE had delayed onset of SLE kidney disease and lower urinary protein excretion. Animals treated with peptides once kidney disease was already established showed prolonged survival and halting of the progression of renal disease. It appears that the mechanism responsible for the effectiveness of this treatment rests in preventing the T cells from sending signals to the B cells that help them make antibodies. The antibodies made to nucleosomes and other host molecules are thought to be important in the development of the kidney failure that occurs in SLE.

Implications: The implications of this work are novel and important in that they may serve as a therapeutic modality to treat patients with established SLE, especially those with SLE nephritis (kidney disease). SLE nephritis is among the most severe, life- and livelihood-threatening manifestations of SLE. Therapies for SLE nephritis are currently limited in scope, nonspecific in targeting, and associated with significant toxicity and morbidity. Autoantigen-derived peptide therapy may prove to be a specific, targeted, and relatively less toxic therapy.

Datta S et al: Antigen-specific therapy of murine lupus nephritis using nucleosomal peptides: Tolerance spreading impairs pathogenic function of autoimmune T and B cells. J Immunology, in press.

Gene Therapy Restored Protective Function in Limb Girdle Muscular Dystrophy

Background: Limb-girdle muscular dystrophies (LGMD) are caused by genetic mutations that disrupt a critical complex on muscle membranes. This sarcoglycan complex helps protect the muscle membrane, or sarcolemma, from disruption during forceful contractions. The sarcoglycan complex spans the sarcolemma and links components of the extracellular matrix to the inside of the muscle cell. The muscle side of the complex binds with the protein dystrophin, which is associated with Duchenne muscular dystrophy. LGMD is recognized as a group of conditions distinct from DMD, but because the genes for the sarcoglycans are considerably smaller than that for dystrophin, researchers have considered them as a test case for gene therapy in muscle.

Advance: Researchers have developed a technique that successfully produces widespread transfer of corrective genetic material into muscle cells throughout an entire limb. Using hamsters with a naturally occurring form of LGMD caused by a defective sarcoglycan subunit, the researchers were able to deliver viruses carrying a normal gene for the defective subunit. The result was stable supranormal expression of the sarcoglycan subunit gene, and muscles that expressed the replacement gene were fivefold less likely to be damaged during forceful contractions than the original defective cells.

Implications: Successful stable gene transfer after either intramuscular or intravascular administration in mature hamsters provides a strong rationale for using adeno-associated virus-derived vectors to treat genetic muscular diseases.

Greelish JP, SU LT, Lankford EB, Burkman JM, Chen H, Konig SK, Mercier IM, Desjardins PR, Mitchell MA, Zheng XG, Leferovich J, GAO GP, Balice-Gordon RJ, Wilson JM, and Stedman, HH: Stable restoration of the sarcoglycan complex in dystrophic muscle perfused with histamine and a recombinant adeno-associated viral vector. Nature Medicine 5, 439-43, 1999.

Low Dose Estrogen Prevents Bone Loss

Background: Estrogen replacement is the cornerstone of osteoporosis treatment and prevention, but there are known side effects (bleeding, thrombotic events, and breast tenderness) with the most common formulation and dose of estrogen and a possible association of long-term use with breast cancer.

Advance: In a randomized, double-blind placebo-controlled trial testing the efficacy of daily low-dose estrogen plus progesterone in older women (over the age of 65), researchers found significant increases in spine, forearm, and total body bone mineral density in the women on low-dose estrogen. (Supplemental calcium and vitamin D were provided to all participants.)

Implications: Because estrogen is currently the first line of defense for osteoporosis and has known side effects, it is critical to use the lowest effective dose that will preserve and even add bone. This study provides important proof of the concept that low-dose estrogen can be an effective preventive and therapeutic option. [secondary B prevention]

Recker RR, Davies KM, Dowd RM, and Heaney RP: The effect of low-dose continuous estrogen and progesterone with calcium and vitamin D on bone in elderly women: A randomized, controlled trial. Annals of Internal Medicine, June 1, 1999, 130:897-904.

Green Tea Products Show Anti-inflammatory Activity in Mouse Models

Background: Rheumatoid arthritis is an inflammatory condition affecting joints, resulting in pain and, over time, destruction of joints. More than 2 million Americans have rheumatoid arthritis. Recently new drugs have been introduced that ameliorate the inflammation of rheumatoid arthritis.

Advance: Investigators fed an antioxidant-rich organic fraction isolated from green tea to mice before treating them with a protocol to induce an inflammatory arthritis. They found that mice fed green tea products were significantly less susceptible to the development of inflammatory arthritis when compared to mice not fed these products.

Implications: This research suggests that identification of common dietary substances capable of affording protection or modulating the onset and severity of arthritis may be used in the future to treat or prevent rheumatoid arthritis.

Haqqi TM, Anthony DD, Gupta S, Ahmad N, Lee M-S, Kumar GK, and Mukhtar H: Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. Proc NAS USA 96, 4524-4529, April 13, 1999.

Guidance for Treating Patients with Brain Aneurysms

Background: A brain or cerebral aneurysm is a weak spot in the wall of a cerebral artery that balloons out due to pressure from the blood. When a brain aneurysm ruptures, it releases blood into the area surrounding the brain (a subarachnoid hemorrhage) causing a hemorrhagic (bleeding) stroke. Hemorrhagic strokes account for about 20 percent of all strokes, but they are more lethal than strokes due to an obstruction of blood flow to the brain, causing about 80 percent of all stroke-related deaths. Surgery can repair aneurysms, but brain surgery carries its own risks, including stroke or infection that can impair mental ability, damage the brain, or even cause death. Perhaps as many as 10-15 million Americans may have intracranial aneurysms at some point in their lifetimes, but most aneurysms do not rupture. The lack of information about the natural history (development risks, size, location, risk of rupture) of unruptured intracranial aneurysms and about the risks of surgery has hampered physicians and patients in deciding whether surgical treatment is warranted in a particular case.

Advance: A new study followed 2621 patients at 53 centers in the United States, Canada, and Europe. The study examined in detail how the size and location of the unruptured aneurysm and the patient=s medical history influence the likelihood that an aneurysm will burst. The researchers also monitored the frequency and severity of problems following surgery for an unruptured aneurysm to gauge the risks associated with surgical intervention. The study found, for example, that the likelihood an unruptured intracranial aneurysm less than 10mm in diameter would burst was exceedingly low in patients without a history of subarachnoid hemorrhage. With this information in hand, patients and their physicians can make a better informed choice about treatment.

Implications: The results provide much needed guidance for the treatment of unruptured brain aneurysms. Each patient=s situation is different, and patients must discuss their prospects with their physicians, but with this new information many patients with small aneurysms and without a history of brain hemorrhages may choose to avoid surgery and be comforted by the prospect of living a normal lifestyle with minimal risk while monitoring the aneurysm.

The International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysmsCrisk of rupture and risks of surgical intervention. NEJM 339:1725-33, 1999.

Cut Nerve Fibers Are Repaired in An Animal Model of Spinal Cord Injury

Background: Nerve cells have elaborate arbors of fibers and processes that extend from their cell bodies. One type of fiber is the axon, which conducts the electrical signals that form the basis for sensory and motor activity. Traumatic injuries to the brain, spinal cord and peripheral nerves often sever or crush axons, so that cells can no longer communicate. This interruption of axonal conductance can result in severe disorders, ranging from muscle weakness to paralysis, and paresthesia (abnormal sensation) to anesthesia (loss of sensation). Injury to the nervous system affects millions of Americans every year and is a leading cause of disability in both children and adults.

After interruption of axonal connections, some regeneration, that is, regrowth of axons, can take place, especially in the peripheral nervous system (the nerves outside the brain and spinal cord). However, the regrowth of axons is slow and inefficient, and reformation of the circuitry needed for return of normal function remains a goal of research.

Advance: Scientists have now taken a different approach to the problem of nerve injury. Rather than attempting to enhance regeneration, they seek to heal the damaged axons. They have developed and tested a procedure to "glue" the severed ends of the axons back together. First they developed a technique using pieces of rat sciatic nerve outside the body. This method rapidly fused separated stumps of severed axons using calcium-free solutions of polyethylene glycol (PEG). Physiological measurements indicated that the resealed axons transmitted electrical signals normally. *In vivo* studies showed that PEG alone can fuse axons, but the natural movement of the animal disconnects the repaired nerves. To ensure a more permanent seal, the investigators incorporated the PEG into a hydrogel which bound to surrounding tissues and kept the axons united. The potential to reseal or reattached injured axons, which prevents the degeneration of axons and reestablishes connections in the nervous system, opens a new avenue for therapies of spinal cord and peripheral nerve trauma.

Implications: Axonal regeneration is an important goal of research to enhance function after trauma to the nervous system. Unfortunately, the barriers to functional regeneration are formidable and include such conditions as inhibitory molecules in the axonal environment, limited capacity for outgrowth of the injured neurons, the great distances over which the axon must extend to its original target, and the absence of trophic factors, the natural chemicals that promote growth and survival. The new approach of resealing ("healing") damaged axons would obviate the need for the complex processes of regeneration, since the severed axon segments would be reconnected.

Lore AB, Hubbell JA, Bobb DS, Ballinger ML, Loftin KL, Smith JW, Smyers ME, Garcia HD, and Bittner GD: Rapid induction of functional and morphological continuity between severed ends of mammalian or earthworm myelinated axons. J. Neurosci. 19: 2332-2454, 1999.

Bionic Rats

Background: Injury to the nervous system, whether by trauma, stroke or by disease, often leaves a person with the ultimate disconnect: a mind that is active, functioning, and alert, but without the nerve connections that allow movement of the body. This absence of mobility has devastating results, turning independence into disability. The ability to use arms and hands to type, eat, comb hair, wave to a grandchild, or answer the phone are gone. Regaining these and the many functions of the upper limbs would improve the quality of life for millions of Americans now afflicted.

Prosthetic devices that rely upon remaining neural function are now available, including cochlear implants for deafness and a system that restores the ability of some persons with spinal cord injury to grasp objects. The success of these systems shows that neural activity can be harnessed and transformed through technology into controlled sensory and motor activity. For persons with more severe disabilities, finding ways for the brain to directly control prosthetic devices holds great promise.

Advance: By wiring directly into the brain, scientists have trained rats to control a robot arm just by thinking about it. First rats were trained in a conventional way to press a lever with their paws to move a robot arm. During this behavior the investigators recorded the activity of several dozen nerve cells through arrays of electrodes implanted in the rats= brains. A sophisticated analysis of the nerve cells= activity revealed a group of cells whose activity predicted the movement of the robot arm. When the signals from these 32 cells were amplified, combined appropriately, and sent directly to the robot arm controller, the rats quickly learned to directly control the arm just by their brains= activity, without using their paws.

Implications: These results have built on decades of research about how the brain controls movement and intensive efforts to develop safe and effective neuroprosthetic devices. The experiments are an important step in moving brain-controlled devices from science fiction to reality, but much work is needed before the technology can be adapted to practical prosthetic devices for human use.

Chapin JK, Moxon KA, Markowitz RS, and Nicolelis MA: Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. Nature Neuroscience 2:64-70, 1999.
With a >news and views= commentary:
Fetz EE: Real-time control of a robotic arm by neuronal assemblies. Nature Neuroscience 2:593-584.

Drug Delivery to the Central Nervous System

Background: The blood brain barrier normally protects sensitive nerve cells of the brain and spinal cord by restricting access of potentially harmful substances from the general circulation. However, the barrier also prevents access of many drugs than might be useful in treating disorders of the brain and spinal cord.

Advance: Neurosurgeons have now developed a method of targeting drugs where they are needed through small tubes introduced into the brain and spinal cord. The method relies on carefully controlled convection, that is, bulk flow of fluid, within the spaces between cells. Using this approach researchers have successfully delivered anticancer drugs to malignant brain tumors in patients and drugs to combat Parkinson=s disease in non-human primates. Most recently, researchers have replaced the enzyme glucocerebrosidase, in the brains of rodents which, like patients with Gaucher=s disease, lack this enzyme. The enzyme appeared to be stable and to be efficiently targeted to the cells that needed it.

Implications: This new approach for drug delivery to the CNS allows precise targeting of drugs where they are needed in the brain and spinal cord. This opens new opportunities for treating many CNS disorders, including tumors, neurodegenerative diseases, epilepsy, spinal cord and brain injury, and inherited enzyme defects, like Gaucher=s disease.

Wood JD, Lonser RR, Gogate N, Morrison PF, and Oldfield, EH: Convective delivery of macro molecules into the naïve and traumatized spinal cords of rats. J. Neurosurg: Spine 90: 115-120, 1999.

Lieberman DM, Corthesy M-E, Cummins A, and Oldfield EH: Reversal of experimental parkinsonism by using selective chemical ablation of the medial globus pallidus. J. Neurosurg 90: 928-934, 1999.

Lonser RR, Corthesy M-E, Morrison PF, Gogate N, and Oldfield EH: Convection-enhanced selective excitotoxic ablation of the neurons of the globus pallidus internus for treatment of parkinsonism in nonhuman primates. J. Neurosurg 91: 294-302, 1999.

Chen, MY, Lonser RR, Morrison PF, Governale LS, and Oldfield EH: Variables affecting convection-enhanced delivery to the striatum: a systematic examination of rate of infusion, cannula size, infusate concentration, and tissue-cannula sealing time. J. Neurosurg 90: 315-320, 1999.

Zirzow GC, Sanchez OA, Murray GJ, Brady RO, and Oldfield EH: Delivery distribution and neuronal uptake of exogenous mannose-terminal glucocerebrosidase in the intact rat brain. Neurochemical Research 24: 301-5, 1999.

Stem Cell Transplants Migrate Throughout the Abnormal Brain and Reduce Disease Symptoms

Backgound: Neural stem cells are immature cells that can multiply and specialize to form the many cell types that make up the brain. For years researchers have been studying neural stem cells isolated from animals and the natural signals that control their proliferation and specialization with the idea that neural stem cells might be useful for treating brain disorders. Several recent findings encourage the hope that neural stem cells might be helpful for disorders in which cell loss is restricted to certain parts of the brain, such as Parkinson=s disease, but the promise for the many diseases in which cell dysfunction is Aglobal@ or spread widely in the brain has been less clear.

Advance: A new study provides the first evidence that neural stem cells can repair damage from brain disorders where cell dysfunction is Aglobal.@ Scientists injected cultured neural stem cells into the brains of newborn Ashiverer@ mice. This strain of mice lacks a key protein needed to form myelin, the essential electrical insulation that surround nerve fibers, and develops severe tremors. Many of the stem cells migrated throughout the brain and matured into oligodendrocytes, the cells that normally form myelin. In 60% of the mice these cells produced enough myelin that the tremors almost completely disappeared.

Implications: Deficiencies of myelin are responsible for several human disorders, including multiple sclerosis and childhood disorders called leukodystrophies, and this study has obvious implications for the possibility of stem cell therapy. The ability of transplanted stem cells to migrate widely opens many other possibilities, including replacing other lost cell types or genetically engineering stem cell to provide therapeutic proteins. However, researchers need to answer many questions before the promise of stem cells is realized. Questions include, for example, whether human stem cells behave similarly to their mouse counterparts, whether transplanted cells will fall victim to ongoing degenerative disease processes, and how to control the specialization of stem cells to replace the types of cells that are lost.

Yandava BD, Billinghurst LL, and Snyder EY: AGlobal@ cell replacement is feasible via neural stem cell transplantation: Evidence from the dysmelinated *shiverer* mouse brain. PNAS 96:7029-34, 1999.

Antibiotics Restore Protein Function in Mouse Model of Muscular Dystrophy

Background: Duchenne muscular dystrophy (DMD) is a progressive degenerative disorder of muscle caused by a mutation in the gene coding for dystrophin, a structural protein of muscle. The gene is on the X chromosome so DMD affects boys, although women who carry the gene may show some signs. No treatment is available to halt the degeneration, and patients die of respiratory or cardiac failure by their teens or early twenties. In about 15% of DMD patients, the mutation is a premature stop codon, that is, an incorrect Acode word@ in the gene that causes the protein synthesizing machinery of the cell to halt, resulting in the absence of dystrophin. The *mdx* mouse model of DMD also results from a premature stop codon, so it is an especially good model for these 15% of DMD cases. For several years scientists have known that certain antibiotics cause misreading of the genetic code and can sometimes suppress premature stop codons by causing the protein synthesizing machinery to misread the stop, insert another amino acid protein building block, and continue.

Advance: A team of scientists first performed an *in vitro* study, in which cultured myotubes (immature muscle cells) from the *mdx* mouse were grown in the presence of the antibiotic gentamicin. These cells made dystrophin, and delivered this protein just inside the outer cell membrane, where it is supposed to be. Then researchers then injected gentamicin in varying doses into *mdx* mice to identify an optimum treatment dosage and gave a daily injection for 2 weeks. Skeletal muscle cells of the mice expressed dystrophin at about 10-20% of the levels in normal mice, and tests showed that this was enough to restore muscle strength to the level of normal mice and to protect muscle cells against degeneration. Even more exciting, dystrophin was also present in the diaphragm and the heart, which are often the most serious concerns in human patients. Although gentamicin is approved for use in humans as an antibiotic, it has serious side effects, including deafness. The researchers used gentamicin in combination with an iron chelator, known to prevent hearing loss, and its effectiveness in restoring dystrophin levels was not compromised.

Implications: This could be a real breakthrough, because it appears that these researchers may have cured some mice that had the animal model of Duchenne muscular dystrophy. The findings have obvious treatment implications for the 15% of DMD boys whose genetic defect is a premature stop codon, and clinical trials are expected to begin soon. In addition, many other genetic disorders may result from nonsense mutations, and these promising results should encourage similar studies in other genetic disorders.

Barton-Davis ER, Cordier L, Shoturma DI, Leland SE, and Sweeney HL: Aminoglycoside antibiotics restore dystrophin function to skeletal muscles of *mdx* mice. Journal of Clinical Investigation 104: 375-381, 1999.
With Commentary: Kaufman RJ: Correction of genetic disease by making sense from nonsense. Journal of Clinical Investigation 104: 367-368, 1999.

Gene Therapy for Muscular Dystrophy

Background: Muscular dystrophies are inherited diseases that lead to progressive weakness and degeneration of muscle, often causing severe disability or death. Several forms of muscular dystrophy are caused by inherited defects in muscle proteins that weaken the muscle membrane and lead to muscle loss. Previous attempts to replace the missing proteins have been unsuccessful because of the difficulty of repairing the millions of muscle cells of the body.

Advance: Now, researchers have successfully replaced a missing protein, called delta-sarcoglycan, in hamsters with muscular dystrophy that accurately mimics a disease in people called limb girdle muscular dystrophy (LGMD). The scientists inserted the gene for sarcoglycan into a virus that had been rendered harmless but retained the capacity to infect muscle cells. They then injected the viral particles into the blood supply to a limb and used histamine, a natural regulator of blood vessels, to trick the blood vessels into becoming temporarily leaky enough to allow the viruses to pass through to the muscle cells. This procedure efficiently protected muscle fibers from degeneration.

Implications: The researchers are now adapting their procedure for clinical trials with humans that have this form of muscular dystrophy. If successful, the same type of procedure might be adapted to several other forms of the disease.

Greelish et al, The restoration of the sarcoglycan complex in dystrophic muscle perfused with histamine and a recombinant adeno-associated viral vector, Nature Medicine 5:439-43 1999.

New Approach to Treating Pneumonia in Immunosuppressed Populations

Background: Pneumocystis carinii is a tiny parasite that preys on those with weakened immune systemsBpremature infants, people with AIDS, people with cancer, and organ transplant recipients. It produces pneumonia in its victims, making them gasp for air and turn eerily blue from lack of oxygen. If not treated, it is almost always fatal.

Fortunately, the disease is currently treatable with an inexpensive antibiotic. But because microbial diseases are becoming increasingly resistant to existing drugs, scientists are always looking for new treatments. A group of basic researchers recently devised an entirely new approach to treating *Pneumocystis carinii* pneumonia.

Advance: Instead of screening a vast range of natural products, which is how most drugs have been discovered, these researchers are specifically targeting the essential core of the parasiteBits genetic material. The researchers focused on RNA, a genetic material that is similar to DNA, but is a step closer to protein synthesis. They designed a short "antisense" RNA molecule that binds to a section of RNA in the organism. This particular section of RNA is an excellent target, because it is critical for the parasite's survival and it is not present in humans, so drugs that target it are less likely to produce unwanted side effects in people.

The synthetic RNA molecule is called "antisense" because its genetic sequence is biochemically complementary toBand therefore binds toBits target, the "sense" molecule. Because the synthetic molecule takes advantage of the shape as well as the sequence of its target, it binds 1,000 to 100,000 times more tightly to the target than would be expected based on sequence alone.

When bound to the target RNA strand, the synthetic RNA disrupts the normal process by which *P. carinii* cells construct protein-making machines called ribosomes. Without being able to properly construct ribosomes, the organism can no longer grow or reproduce and thus loses its ability to cause disease.

Implications: Because the synthetic RNA molecules produced by these researchers are small (6 nucleotides long, rather than the typical 15-20 used in similar strategies), they are easier and cheaper to synthesize. The researchers also modified the molecule to resist degradation by enzymes in the human body.

Although the work was done in a laboratory environment, rather than in people, the success of the work proves that the approach is worth pursuing. Researchers may find additional targets in *P. carinii*, and may also find important RNA targets in other disease-causing microbes.

Testa SM, Gryaznov SM, and Turner DH: In vitro suicide inhibition of self-splicing of a group I intron from *Pneumocystis carinii* by an *N* 3' --> *P* 5' phosphoramidate hexanucleotide. Proc. Natl. Acad. Sci. USA, 96: 2734-9, 1999.

Control and Prevention of Type 1 Diabetes is Demonstrated in Mice

Background: Diabetes mellitus affects an estimated 16 million people in the United States. Of this number, approximately 800,000 people have type 1 diabetes, an autoimmune disease in which the body=s immune system attacks its own insulin-producing beta islet cells in the pancreas and destroys them. The pancreas then produces little or no insulin, requiring the individual to receive their insulin from an external source to survive. T-cells, critical cells activated in the immune response, invade the pancreas and treat one or more protein components of the insulin-producing beta cells as antigens, or foreign substances, to be destroyed. The identity of self proteins in the pancreatic islets, which may target cells for autoimmune destruction, and their role in the development of diabetes, has long been debated. One of the principal antigens thought to be involved in this response is glutamic acid decarboxylase (GAD), a single self protein expressed by the pancreatic beta cell in diabetes and found in both humans and nonobese diabetic (NOD) mice, a good animal model of human type 1 diabetes. There are two forms of GAD (GAD65 and GAD67); both forms are expressed in the beta islet cells, although their function there is not clear. Some of the earliest antibodiesBproteins produced by the body to protect itself against foreign substancesBfound in prediabetic patients are GAD-specific. Further, administration of GAD65 to NOD mice in some cases significantly delayed the onset of diabetes. This information suggests that GAD is involved in the development of diabetes and that possible use of GAD65, or protein fragments (peptides) of this molecule, may be effective as a form of therapy for type 1 diabetes, termed immunotherapy. To determine the role of GAD in diabetes, researchers examined the effect of selectively suppressing expression of the GAD protein in NOD mice.

Advance: Researchers studied the role of GAD in the development of diabetes by generating NOD mice with added genetic information (transgenic mice) in which expression of GAD was prevented. Researchers observed a correlation between the presence of GAD protein in beta islet cells and the development of diabetes. Animals in which GAD expression was blocked completely remained free of diabetes while those animals that expressed GAD, even at low levels, developed diabetes. In addition, complete suppression of GAD expression blocked the generation of the T cells normally activated in the development of diabetes and protected islet grafts from autoimmune injury. These findings indicate that beta cell GAD expression is essential for the development of type 1 diabetes in the NOD mouse model.

Based on this data, immunotherapy using peptide components of GAD could provide a strategy by which to selectively suppress the T cell-mediated destruction of beta cells and prevent type 1 diabetes. Accordingly, another group of researchers investigated whether a panel of immune responsive sites found on the T cell, called epitopes, could prevent type 1 diabetes. All of the epitopes tested effectively prevented inflammation of the islets (insulitis) and diabetes when administered to NOD mice before the onset of insulitis. However, only a mixture of two of the epitopes prevented progression of insulitis and type 1 diabetes in NOD mice exhibiting more advanced beta cell destruction. GAD-specific peptide immunotherapy required production of the cytokine IL4 to be effective. These findings demonstrate that GAD65- specific peptide immunotherapy can effectively suppres progression to diabetes in the NOD mouse, dependent on the epitope targeted and the extent of preexisting beta cell destruction in the patient.

Implications: The demonstration that GAD expression is required for the development of autoimmune diabetes and that certain GAD epitopes can suppress progression from insulitis to overt diabetes in the NOD mouse is a major step toward development of new therapies and preventive strategies for type 1 diabetes. Because of its many similarities with the disease in humans, the NOD mouse model enables the benefits of new therapeutic strategies to be firmly established before being tried in humans. While the study demonstrates the feasibility of peptide-based immunotherapy, it should be remembered that in a human clinical trial the peptides that are going to be recognized by T cells may be different from those recognized in mice. Even so, the promise of the work for the prevention of type 1 diabetes is significant and must be pursued. The number of people with type 1 diabetes is approaching one million in this country and some 15 million worldwide. New approaches to treatment and prevention for this disease are desperately needed. [secondary B prevention]

Yoon J-W, et al.: Control of Autoimmune Diabetes in NOD Mice by Suppression of GAD Expression in β Cells. Science (1999); 284:1183-1187.

Tisch R, Wang B, and Serreze DV, Induction of glutamic acid decarboxylase 65-specific Th2 cells and suppression of autoimmune diabetes at late stages of disease is epitope dependent. J Immunol 1999;163(3):1178-87.

Safe and Effective Delivery of Therapeutic Proteins by Gene Therapy

Background: Gene therapy is a novel approach to combating diseases based on modifying the expression of a person=s genes in an attempt to treat, cure, or ultimately prevent disease. The challenge in gene therapy is to develop approaches for delivering therapeutic materials to the cells of a patient in a way that is specific, efficient and safe. To do this, researchers have developed gene delivery vehicles called vectors. Two viral vectors currently employed in the field of gene therapy are adenoviral vectors and adeno-associated viral (AAV) vectors. Virus have evolved a way of encapsulating and delivering their genes to human cells. Scientists have tried to take advantage of virus biology to manipulate its genetic material to remove the viral genes and insert therapeutic genes. Once inside the cell, the altered gene must operate correctly, regulating precisely the timing and dosage of the therapeutic protein expressed. This may be done through the development of a vector that contains both the protein-producing gene and a Amolecular rheostat@ that would react to external stimuli to regulate expression of the desired protein.

Advance: NIH researchers and the biotechnology industry have developed a system to do just this. In their system, two vectors were usedBone to deliver the target gene and the other to deliver the Amolecular rheostat@ or regulatory agent. Investigators then explored the potential of this system to enable the long-term expression of human growth hormone (hGH) when introduced into mice, using either a set of adenoviral vectors or a set of AAV vectors. Upon delivery of either vector system into normal mice and into mice lacking a functioning immune system (immunodeficient), hGH expression was detected only after the administration of rapamycin, the regulatory agent. The precise level and duration of hGH expression could be directly controlled by the rapamycin dosing regimens. Use of the AAV vectors allowed for stable expression of hGH, even after many months, in both the normal and immunodeficient mice whereas the adenovirus-directed expression of hGH was extinguished in the normal mouse. This suggests that there were still components of the adenoviral system that induced a destructive cellular immune response in the mouse. Investigators concluded that AAV is the preferred vector for long-term, systematic protein delivery.

Implications: These studies demonstrate that the rapamycin-based regulatory system, delivered by AAV, fulfills many of the crucial requirements necessary for the safe and effective delivery of therapeutic proteins by gene therapy. Protein expression is induced by an orally available drug and the protein can be delivered at the desired concentration by controlling rapamycin dose. Importantly, in the absence of rapamycin, protein expression is undetectable. Furthermore, regulated protein expression was detectable for many months. Finally, as the system is made up of human components, the potential of initiating an immune response in the patient is limited.

Rivera VM et al., Long-term Regulated Expression of Growth Hormone in Mice After Intramuscular Gene Transfer. , PNAS 1999; 96:8657-62.

Infliximab for Crohn=s Disease: A Randomized, Blinded, Controlled Clinical Trial

Background: Crohn=s disease is a chronic inflammatory bowel disease of unknown cause. In about a third of the patients, fistulas develop; these are perforations of the bowel wall that connect to other tissues such as bowel, bladder, or vagina, or extend through the abdominal wall or the anal skin (perianal) area. They tend to leak, or drain, fluids, risking infection. Fistulas that extend through the abdominal wall or into the perineum are a serious complication of Crohn=s disease and are difficult to treat. These fistulas rarely heal spontaneously or with drug treatment and often require surgery. Previous research has shown a role of Tumor Necrosis Factor-Alpha (TNF-α), a hormone-like local factor (a cytokine) produced in increased amounts in the intestinal mucosa of patients with Crohn=s disease; the question became whether neutralization of TNF-α might prove to be a therapeutic intervention for these patients, as has been suggested for several chronic inflammatory diseases. Infliximab (Remicade) is an antibody to tumor necrosis factor-α, and has now been developed as a treatment for Crohn=s disease; this is the first drug ever approved by the FDA for the treatment of inflammatory bowel disease.

Advance: A randomized, multicenter, double-blind placebo-controlled trial of infliximab for the treatment of fistulas in patients with Crohn=s disease was conducted with the primary end point of reducing by 50 percent or more the number of draining fistulas. Sixty-eight percent of patients receiving 5 mg of infliximab per kilogram and 56 percent receiving 10 mg per kilogram achieved the primary end point as compared with 26 percent of patients in the placebo group. In addition, 55 percent of patients taking 5 mg of infliximab per kilogram and 38 percent of those assigned to 20 mg per kilogram had closure of all fistulas, as compared with 13 percent of those assigned to placebo. The therapeutic effect of infliximab is due to its blockage of the inflammatory agent (the cytokine TNF-α). It was concluded that infliximab is an efficacious treatment for fistulas in patients with Crohn=s disease; it is the first drug to be effective in closing skin fistulas.

Implications: This is one of the major success stories in current medicine, involving the first FDA-approved treatment for Crohn=s disease. It had been found in other clinical studies to be safe and effective in the treatment of moderate to severe disease, and this well-designed clinical trial has shown its effectiveness in treating and reversing the serious complication of fistula formation. Inflammatory bowel disease affects some 500,000 people in the United States, and causes about 700,000 visits to physicians and 100,000 hospital discharges each year.

Present, DH, et al., Infliximab for the Treatment of Fistulas in Crohn=s Disease. New England Journal of Medicine (1999); 340:1398-405.

The Treatment of Chronic Hepatitis C

Background: Until recently, interferon alfa (an antiviral protein) was the only therapy available for those infected; however, only 15 to 20 % of patients with chronic hepatitis C have a sustained response to interferon therapy alone. Previous evidence suggested that combining interferon with ribavirin (an antiviral drug similar in structure to a nucleic acid component) might be more effective than interferon alone.

Advance: The present study was designed to compare the safety and efficacy of interferon alone and in combination with ribavirin for the initial treatment of chronic hepatitis C and to determine the optimal duration of combination therapy. The results showed again that only 15 to 20 % responded to interferon alone. Combination therapy for either 24 or 48 weeks was superior to interferon alone, judging by virologic, biochemical, and tissue (histologic) effects. Late clearance of the viral genetic material (RNA) from the serum was now seen, as part of a sustained response to the treatment (often lasting 5 to 10 years). For one strain of the virus (HCV genotype 1) the best results occurred in those treated for 48 weeks; with this strain, as with cases with high viral load, advanced fibrosis, or cirrhosis, treatment has historically been unsuccessful. Combination therapy was relatively safe, but its use more often required dose reductions or discontinuance than use of interferon alone.

Implications: This research indicates that treatment of chronic hepatitis C with a combination of interferon and ribavirin is more effective than interferon alone, and that the combined therapy is indicated as the initial therapy for these patients. Chronic hepatitis C infection is now recognized as an important health care problem. In the United States, infection with hepatitis C virus (HCV) is a leading cause of chronic liver disease and the most common indication for liver transplantation. Nearly four million people are estimated to be infected, and of this number approximately 20% will eventually develop cirrhosis of the liver. The beneficial effect of combination therapy has major implications for patients in whom treatment has previously been unsuccessful. A safe and effective therapy of hepatitis C would decrease the mortality and morbidity of liver disease considerably. The expectation is that with current therapies, 30-40 percent of patients may be cured of this chronic viral infection and liver disease.

McHutchison JG et al., Interferon alfa-2b Alone or in Combination with Ribavirin As Initial Treatment for Chronic Hepatitis C. N Engl J Med 1988; 339:1485-92.

Growing Body of Evidence Identifies Efficacy of Alternative Pain Management Techniques

Background: Decades of research have proven the benefit of opiates and non-narcotic pharmacological therapies for the effective management of pain. There are, however, conditions both chronic and acute for which pain management is an elusive goal. Many reasons account for this lack of success, including our incomplete understanding of the biochemical processes that induce pain. Confounding the physiological circumstances, there is ample evidence that the psychological state of an individual contributes to their perception of pain. Anxiety often accompanies pain. Identifying new medications to block pain, and finding ways to reduce the anxiety associated with it, are important issues to resolve as researchers develop more effective pain management regimens.

Advance: In the last year, several groups have reported success in reducing pain using acupuncture either alone or in conjunction with medication for conditions as diverse as osteoarthritis and fibromyalgia and following oral surgery. Another study showed that therapeutic touch reduced the intensity of chronic pain and its associated anxiety in elderly patients. Together, these studies show that alternative pain management techniques can complement the development of improved pain management strategies.

Implications: Prevailing pain management practices in medicine focus on the use of the ever-increasing number of narcotic and non-narcotic analgesics. While this approach has been quite successful for many people with varying conditions, there remains a considerable population for whom medication is partially successful and others for whom there is a concern of addiction. The ability to introduce techniques like therapeutic touch and acupuncture to expand the pain management spectrum provides an opportunity to complement the use of medications for conditions like osteoarthritis. Perhaps more importantly, applying these techniques has the potential to concurrently reduce both pain and anxiety in those instances in which medication alone is not having the desired effect.

Lin Y, Taylor A,: Effects of Therapeutic Touch in Reducing Pain and Anxiety in an Elderly Population. Integrative Medicine. 1:4: 155-162, 1998.

Berman, BM, et al. : A Randomized Trial of Acupuncture as an Adjunctive Therapy in Osteoarthritis of the Knee. Rheumatology. 38: 346-354, 1999.

Lao L, et al.: Evaluation of Acupuncture for Pain Control After Oral Surgery, Arch Otolaryngol Head Surg: 125 567-572, 1999.

Berman BM, et al.: Is Acupuncture Effective in the Treatment of Fibromyalgia. J Am Family Practice 48:3: 213-18, 1999.

New Treatment for Uveitis May Improve Vision and Quality of Life

Background: Uveitis is an inflammation inside the eye that affects primarily children and young adults. People with anterior uveitis, which affects the front of the eye, frequently have pain, red eyes, and light sensitivity. People with intermediate and posterior uveitis (as in this study), which affects the back of the eye will complain of blurred vision. The inflammation caused by uveitis can be due to an infection or can be noninfectious; the cause is frequently unknown. Not all inflammation indicates infection. Uveitis is often a reflection of diseases occurring elsewhere in the body. While it is difficult to assign a specific number to people who suffer from uveitis, it is estimated that the disease is responsible for about 10 percent of all visual impairment in the United States. If left untreated, uveitis can cause blindness.

Advance: Scientists conducted a study to evaluate the safety and potential usefulness of a monoclonal antibody that is directed against a receptor on immune cells. These receptors bind to a product of the immune system, Interleukin-2. Interleukin-2 plays an important role in activating immune cells, and therefore plays a central role in an inflammatory response in the body. This antibody was given to patients with uveitis thought to be due to autoimmunity and not to an infection. All patients who entered the study needed systemic immunosuppressive agents to control the inflammation in their eyes, and to maintain relatively good vision. Once patients received the monoclonal antibody (Zenapax) they were slowly weaned off their standard immunosuppressive medications. Nine of the ten patients who entered the study were able to stop their regular medication, ultimately receiving antibody therapy once a month. All patients tolerated the medication so that there was no need for a dose reduction. This is the first long term use of this antibody for an autoimmune disease. The results would suggest that anti-Interleukin-2 receptor therapy may be an effective therapeutic approach to the treatment of uveitis, as well as other autoimmune conditions, with potential improvement of vision, as well of the quality of life for patients.

Implications: The treatment of sight threatening uveitis involving the middle and back portions of the eye often requires strong drugs that affect the immune system. These are usually given by mouth and serious side effects may be seen. Side effects may include: brittle bones, kidney damage, opportunistic infection, cataracts, glaucoma, sterility, or gene damage. Patients found a dramatic improvement in the quality of life with their taking medication only once a month as opposed to several pills every day. This approach to autoimmune disease may possibly be more or equally as effective as everyday therapy and might have application in other disorders that are autoimmune and non-infectious in nature, such as multiple sclerosis and psoriasis.

Nussenblatt RB, Fortin E, Schiffman R, Rizzo L, Smith J, VanVeldhuisen P, Sran P, Yaffe A, Goldman C, Waldmann T, and Whitcup S: Treatment of noninfectious intermediate and posterior uveitis with the humanized anti-Tac mAb: a phase I/II clinical trial. Proc Natl Acad Sci 96(13):7462-6, 1999.

Electrical Stimulation of the Paralyzed Larynx

Background: Paralysis of the voice box, or larynx, is a serious problem that is often a complication of head and neck surgery. When the larynx is paralyzed, voice production and protection of the airway are compromised. Current treatment modalities provide less than ideal options for individuals faced with this disorder. In cases of bilateral paralysis, the airway can be enlarged by several techniques. However, all of these current techniques may compromise voice production and airway protection, which have consequences for both the health and the quality of life for the patient. In 1976, electrical stimulation of the muscles of the larynx was proposed as an alternative treatment for paralysis of laryngeal or other head and neck muscles. Over the last decade, NIH funding has allowed this approach to be explored and refined in animal models. As a result, many basic issues have been addressed: can a denervated muscle be maintained by the stimulation? What is the most effective stimulus paradigm? What are the long-term effects of stimulation on the muscle biochemistry and physiology? Does stimulation have any effect on the eventual reinnervation of muscle?

Advance: The first human clinical trial of electrical stimulation of a posterior cricoarytenoid (PCA) laryngeal muscle was performed in a patient using an external stimulation device. The success of this trial led to the first implantation of an electrical stimulation device in a patient in 1996. As described in a manuscript resulting from this work, electrical stimulation of muscles moving the vocal folds restored ventilation to the patient without harming voice quality or airway protection. Subsequent to implantation of the electrical stimulator, the patient=s breathing, speech production and external appearance are normal without any sign of laryngeal paralysis.

Implications: These studies are providing a foundation for the use of electrical stimulation as a treatment modality for paralysis of laryngeal muscles, as well as other head and neck muscles.

Manuscript in preparation to be submitted to New England Journal of Medicine.

Zealear DL, Billante CL, Courey MS, Ossoff RH and Netterville JL: Electrical pacing of the paralyzed human larynx with an implantable device. In Proceedings of the 4th Annual International Functional Electrical Stimulation Society, Sendai, Japan In press.

Identifying the Most Effective Infertility Treatment

Background: Infertility affects approximately 15% of U.S. couples. In many cases, a specific diagnosis cannot be made, so treatments are given on an empirical or trial-and-error basis. These treatments can be invasive and/or costly, yet we don=t know much about determining the most appropriate treatment for each individual patient.

Advance: In a large randomized controlled clinical trial, the efficacy of two common treatments, superovulation (stimulation of the ovary to produce eggs) and intrauterine insemination (the introduction of specially prepared sperm directly into the uterus), was compared to that of the traditional therapy, insemination at the cervix. The investigators tested 932 couples who were unable to conceive a child, despite the fact that the woman appears normal and her male partner produces at least some sperm. The trial had four treatment groups. In the control group, the women did not receive any drugs to induce ovulation and were inseminated in the cervix (intracervical insemination) at the time of ovulation. In the second group, the women received no ovulation-inducing drugs and were inseminated in the uterus (intrauterine insemination) at the time of ovulation. The third group of women received injections of follicle stimulating hormone (FSH) to induce ovulation, and then received intracervical insemination. The fourth group of women received FSH injections and then intrauterine insemination.

The group receiving FSH injections and intrauterine insemination had the highest rate of pregnancy at 33%. Women receiving FSH injections and intracervical insemination had almost half that pregnancy rate at 19%. Those receiving intrauterine insemination during natural ovulation had a pregnancy rate of 18%, and those receiving the traditional intracervical insemination during natural ovulation achieved a pregnancy rate of 10%. Thus, couples receiving both test treatments combined were almost 3.5 times as likely to achieve pregnancy, compared to the traditional intracervical insemination group. Although this combined therapy is costly, with induced ovulation averaging $1300 per cycle, it is considerably less expensive than many other fertility treatments.

Implications: This study provides evidence to clinicians that a combination of superovulation and intrauterine insemination is effective in achieving conception in infertile couples with an apparently normal female partner. This finding allows physicians to recommend this combination to couples seeking treatment for infertility and provides an alternative to invasive and expensive techniques such as *in vitro* fertilization. Furthermore, by increasing the chances for success, total costs for a successful treatment may be reduced. Other treatment options may be appropriate for given subgroups of patients, a subject for further research. Couples should be informed by their physicians of all treatment options and their chances of success, as well as their costs and complications.

Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, Hill JA, Mastroianni Jr L, Buster JE, Nakajima ST, Vogel DL, and Canfield RE. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. N Eng J Med 340: 177-83, 1999.

Understanding the Causes of Preeclampsia

Background: The placenta is a specialized organ that is critical to the maintenance of pregnancy. Abnormalities in placenta function can lead to life-threatening conditions for both mother and fetus. One such condition, preeclampsia, is a disorder that adversely affects approximately 7-10% of first-time pregnancies and is the leading cause of maternal death in the U.S. Besides causing dangerously high blood pressure, kidney failure, and seizures in the mother, children born to mothers with preeclampsia may be born prematurely or may have a low birth weight. The cause of the condition is unknown. One hypothesis is that it results from poor blood vessel development between the placenta and the uterus. Another hypothesis is that an imbalance between chemicals that raise (thromboxane) and lower (prostacyclin) blood pressure in pregnancy causes preeclampsia.

Advance: In two separate studies, researchers have made substantial contributions to understanding normal and abnormal functions related to preeclampsia. In one study, researchers have uncovered basic mechanisms involved in the normal formation of blood vessels between the placenta and uterus and have shown that certain aspects of these mechanisms are different in preeclampsia. In addition, these investigators have shown that specialized placental cells (cytotrophoblasts) in direct contact with uterine cells undergo a high rate of apoptosis, or Acellular suicide,@ in preeclamptic placentas compared to normal ones. Consequently, the placental connection between the mother and the fetus is compromised.

In another study, researchers collected urine samples from a large population of women early in pregnancy. Those who developed preeclampsia and a comparison group of normal pregnant women had these samples tested for the chemicals prostacyclin and thromboxane after they gave birth. The study revealed that prostacyclin levels are significantly lower in women destined to develop preeclampsia months before symptoms appear, and that the ratio of thromboxane to prostacyclin is elevated in women who develop preeclampsia, from the second trimester onward. Thus, subnormal prostacyclin and thromboxane-prostacyclin ratio abnormalities play a key role in developing clinical preeclampsia, either as a cause or an early abnormality.

Implications: These important discoveries provide significant new information on the cause of preeclampsiaBsuggesting possible avenues for early diagnosis and prevention of a potentially fatal condition. In addition, results from one study have already laid the foundation to develop possible treatments for this condition. For example, previous trials have tried, often unsuccessfully, to prevent preeclampsia by giving aspirin to block thromboxane. Now, researchers have developed an important new strategy for preventing preeclampsia that focuses on increasing levels of prostacyclin, rather than blocking thromboxane.

Mills JL, DerSimonian R, Raymond E, Morrow JD, Roberts LJ, Clemens JD, Hauth JC, Catalano P, Sibai B, Curet LB, and Levine RJ: Prostacyclin and thromboxane changes predating clinical onset of preeclampsia: A multicenter prospective study. JAMA 282: 356-62, 1999.

DiFederico E, Genbacev O, and Fisher SJ: Preeclampsia is associated with widespread apoptosis of placental cytotrophoblasts within the uterine wall. Am J Pathol 155: 293-301, 1999.

Risk Factors Among Women After Coronary Artery Bypass Grafting

Background: Although only 27% of the total number of coronary artery bypass grafting (CABG) procedures were performed on women in 1994, there are increasing numbers of women choosing CABG as their treatment for coronary heart disease. Long term outcomes of CABG among women are worse than for men: women have less relief of angina (chest pain), shortness of breath, report poorer levels of health, have more restricted-activity days, more psychosocial impairment and are more likely than men to be using cardiac medications after surgery. Given that coronary heart disease (CHD) is the leading cause of death among women, it is important to know as much as possible about how CHD risk factors change among women over time.

In this study, women having a first-time, isolated CABG were examined for risk factors present at the time of hospitalization, and again one year after surgery. The study found that women one year after CABG continued to have a high prevalence of risk factors for CHD. That is, a large percentage of women continued to be obese, hypertensive, consumed diets high in saturated fats and had suboptimal blood lipid profiles. This finding is in spite of many years of systematic studies which demonstrate the effectiveness of comprehensive risk factor modification in the management of CHD.

Advance: This study confirmed that the principles of the Secondary Prevention Panel of the American Heart Association have not been achieved nor have the findings of the Coronary Artery Surgery Study been improved among women admitted for CABG. This study confirms the need for aggressive and ongoing comprehensive, coordinated focus on coronary heart disease risk factors in women following CABG surgery.

Implications: Women after CABG need aggressive attention paid to their risk factors for CHD. Outcomes would include better control of troublesome symptoms of pain, shortness of breath and reduced-activity days. Possibly reduced utilization of costly primary and secondary care, including rehospitalizations, would be the outcome for patients who came improve their risk factor profile. There are existing models of care wherein nurses who maintain close contact after discharge from the hospital have implemented systematic treatment plans to manage risk factors of CHD: high cholesterol, smoking, hypertension and others. Current modes of care delivery (such as traditional office practice or HMO) have the potential to provide more comprehensive and long-term focus on risk factor modification.

Allen JK. Coronary risk factors in women one year after coronary artery bypass grafting. Journal of Women=s Health and Gender-Based Medicine 8:617-622, 1999.

Controlling Postoperative Pain with Less Medication

Background: Each year, 23 million people undergo surgery in the U.S. Despite the use of pain medication, patients experience moderate to severe pain at rest that increases during ambulation. Pain that is not adequately treated or is untreated has serious consequences: increased stress responses, impaired tissue healing, slowed recovery and interference with sleep and appetite. Better pain management can improve patients' quality of life, reduce length of hospital stay or stay in ambulatory surgery department, as well as decrease the recovery time of patients. People who have had bad experiences with inadequately treated pain may delay diagnosis and treatment for conditions that require some painful procedures. It stands to reason that better pain management is likely to mean fewer delays of patients seeking diagnosis and treatment. This clinical study evaluated the use of music and relaxation as adjuvants (additional measures) to pain medication. Patients were randomized to the treatment and control groups and patients were evaluated before and after the interventions.

Advance: Relaxation, music, and their combination reduced pain more than patient-controlled analgesia alone at ambulation and at rest on the first two postoperative days. The study adds clinical laboratory findings to the consensus recommendations developed in 1992 which recommended increased use of non-pharmacological methods of acute pain control.

Implications: The findings hold promise for expanding the practices used in acute pain control. The study holds promise for good pain control with the added benefit of reduced use of analgesic drugs. All of these changes in practice are easily attainable without requirements for more technology. Patients are likely to perceive self-managed control of postoperative pain as empowering.

Good M, Stanton-Hicks M, Grass JA, Anderson GC, Choi C, Schoolmeesters LJ, Salman A: Relief of postoperative pain with jaw relaxation, music and their combination. Pain 83:163-172, 1999.

Reducing the Burden of Caregivers of Persons with Dementia

Background: For as long as caregiving has been documented, families continue to provide the overwhelming bulk of home care for frail, disabled or demented individuals. Most family members who are caregivers perform other roles as well: raising families, working for employers and participating in religious and civic activities. Being a caregiver is linked with health and mental health problems: higher than usual psychotropic drug use, social isolation, family stress and depression. Often a major source of caregiver stress and burden are the behavioral problems of the family members who are cared for: wandering, agitation, depression, disturbed eating patterns, for example. Despite the high costs of caregiving in terms of their time, their health and their money, most family members who are caregivers want to retain the role. Relevant for public policy, the work of caregivers delays institutionalization of those who are cared for at home.

Other studies show that how caregivers= perceive their ability to handle care recipients= disruptive behavior is important in the caregivers=estimates of their stress and burden. Family disharmony and lack of support also contribute to overall caregiver burden. To address these complex issues, an interdisciplinary psychoeducational seven-week workshop for randomly assigned primary caregivers and other family members was designed to provide information and behavior management training. Five months after the workshop, there were still positive effects among participants: reduced caregiver depression scores, less negative responses to care receivers= disruptive behaviors and a moderate decrease in perceived caregiver burden. These results occurred even though the care recipients= dementia continued to progress as is usual with dementia.

Advance: Findings from this research indicate that a stand-alone educational workshop which provides information and behavioral management techniques for caregivers and families of caregivers can lead to reduced caregiver stress and burden. Information provided in this workshop enabled caregivers to provide sophisticated care tasks.

Implications: The public policy outcomes of reduced caregiver stress and burden include: delayed institutionalization of care recipients, reduced caregiver health needs and reduced caregiver mental health needs. There is potential for more positive outcomes if the intervention described in this study were to be integrated into comprehensive, coordinated systems of community-based care. Chronic diseases of other types which may involve long-term caregiving also may benefit from the intervention described in this study.

Ostwald, SK, Hepburn, KW, Caron, W, Burns, T, Mantel, R: Reducing caregiver burden: a randomized psychoeducational intervention for caregivers of persons with dementia. Gerontologist 38:3, 299-309, 1999.

Successful Ventilator Strategy Found for ARDS Patients

Background: Acute Respiratory Distress Syndrome (ARDS) is a devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. Approximately 150,000 Americans are affected each year, and more than 40 percent of them die. Patients are treated in an intensive care unit, with use of a mechanical ventilator and supplemental oxygen to help them breathe. Mechanical ventilators deliver breaths of oxygen-enriched air to the body and remove breaths of carbon dioxide produced by the body. Earlier laboratory studies suggested that small breaths from the ventilator might not remove sufficient carbon dioxide and that large breaths might damage lung tissue. Several small clinical trials failed to show clearly whether either approach was better.

Advance: Recently, a large clinical trial of mechanical ventilator use for intensive care patients with ARDS showed approximately 20 percent fewer deaths among patients receiving small (6 ml/kg body weight), rather than large (12 ml/kg body weight), breaths of air from a mechanical ventilator. The results were so persuasive that the trial was stopped early so that critical care specialists could be informed.

Implications: Finding a treatment for ARDS has challenged researchers. This is the first time a large multicenter trial has shown that any form of treatment for ARDS could reduce mortality. These results will improve the care of ARDS patients and save thousands of lives each year. The NIH ARDS Clinical Network, a consortium of 10 clinical centers including 24 hospitals, developed and performed the study. The network was formed in 1994 to ensure that multiple large treatment studies on ARDS could be designed and conducted quickly. The ARDS Network is currently conducting several other studies, including two trials of anti-inflammatory drugs for ARDS, that hold promise for future additional improvements in the treatment of ARDS patients.

Press release: NHLBI Clinical Trial Stopped Early: Successful Ventilator Strategy Found for Intensive Care Patients on Life Support, March 15, 1999. NHLBI Communications Office, NIH.

Treating Chronic Pain With Fewer Side Effects

Background: Although opiate medications such as morphine are critical for the treatment of chronic pain, their usage remains limited by the development of tolerance and physical dependence. Considerable research efforts are now being devoted to the development of medications that can effectively treat pain with few or no side effects. One promising area of research attempts to make modifications to opiate compounds that will maintain their analgesic properties, while reducing the undesirable side effects. Opiates act on several different types of sites or receptors on nerve cells in the brain. The specific effect that an opiate has depends on which type of receptor it binds to. By taking an opiate compound that has a particular effect at one type of receptor and modifying its chemical structure scientists hope to develop a better pain medication.

Advance: Scientists have now developed a new opiate compound called DIPP-NH2 that can both activate and inhibit receptors simultaneously, meaning it likely has low abuse potential. When this molecule was tested on laboratory rats, it was found to be three times more potent at producing analgesia than morphine. Furthermore, it produced no physical dependence and less tolerance than morphine when given chronically at high doses.

Implications: The production of this opiate compound opens exciting new avenues into the treatment of chronic pain. Although further research is needed, the results of this study suggest that carefully designed new opiate compounds may be extremely effective in treating pain, but without some of the side effects that limit their use. This could have far reaching effects for the millions of people who suffer from chronic pain. An additional benefit of this compound is its potential as a research tool. Because it produces analgesia without dependence, it will be a very useful tool in understanding the basic brain mechanisms that are involved in addiction. This could in turn facilitate the development of more effective treatments for addiction to opiates such as heroin.

Schiller PW, Fundytus ME, Merovitz L, Weltrowska G, Nguyen T, Lemieuz C, Chung NN, and Coderre TJ: The opioid μagonist/δ antagonist DIPP-NH_2[Q] produces a potent analgesic effect, no physical dependence and less tolerance than morphine in rats. J. Medical Chemistry, In Press.

Treating Chronic Pain With Gene Therapy

Background: Chronic pain is a major health problem that can substantially diminish quality of life and reduce an individual-s productivity. While acute pain, such as that following surgery, is fairly easily treated, chronic pain is very difficult to treat. One of the reasons that chronic pain may be so difficult to treat is that it may cause changes in the brain and spinal cord that actually help to maintain and even increase the pain. Unlike acute pain, which is adaptive, in that it signals that there is a problem that needs attention (i.e. remove foot from tack), chronic pain has no adaptive functions. Furthermore, it can last for years and leave the sufferer completely debilitated. Consequently, significant research is focused on understanding and developing effective treatments for the management of chronic pain.

Advance: Researchers have recently developed a new method of pain control using a novel genetic therapeutic approach. Briefly, researchers applied to the skin of mice a genetically engineered virus that contained genes that code for the production of enkephalins. Enkephalins are chemicals that are naturally produced in the brain and spinal cord and have a function in helping to control pain. The virus was then picked up by nerves and carried to a part of the spinal cord that is involved in sensing pain. Once at this site, the virus began producing a large amount of enkephalins. Following the treatment, the mice appeared normal, and responded normally to acute pain. However, the animals showed a dramatic reduction in their response to chronic pain. In fact, there was a complete elimination of sensitivity to procedures that would normally produce chronic pain.

Implications: While more studies are needed, these results indicate that this type of treatment can successfully treat chronic pain while not impacting an animals ability to respond to acute pain situations. Furthermore, this approach is not invasive and it may offer long-term treatment of chronic pain. This study provides yet another possibility for a substantial contribution of gene therapy to the treatment of health problems. This approach may eventually lead to a noninvasive, safe, and effective treatment of chronic pain in humans.

Wilson, SP, Yeomans, DC, Bender, MA, Lu, Y, Goins, WF, and Glorioso, JC: Antihyperalgesic effects of infection with a preproenkephalin-encoding herpes virus. Proceedings of the National Academy of Science Vol. 96, Issue 6: 3211-3216, 1999.

A New Drug Application Filed with the FDA for a Medication to Treat Heroin Addiction

Background: Addiction to heroin and other opiates is a major public health problem in the United States. In addition to the well-known health, social service and criminal justice costs associated with heroin addiction, injection drug use and sexual activity in this population is a major source of infection for HIV/AIDS, hepatitis, and tuberculosis. To date, methadone has been the major pharmacological agent available to treat heroin addiction. Although methadone treatment is highly effective, it continues to be strictly regulated by Federal, State, and local authorities. For example, regulations require daily attendance, but dosing can only be provided at approved methadone treatment clinics, which are nonexistent in some states, or are in geographic locations that are not readily accessible. As a result, there are many persons in need of treatment who cannot obtain it.

Advance: Basic research exploring the mechanisms of brain receptors and opiate pharmacology has taken a giant step forward by NIH-supported scientists who are working to develop a new treatment medication for opiate addiction. In particular, scientists are testing whether the partial agonist buprenorphine could be combined with naloxone to produce a tablet which would safely and effectively treat heroin and other opiate addiction, have low diversion potential, and be aversive to injection. A number of recent studies have shown that buprenorphine maintenance is an effective treatment for heroin addiction. All testing was performed under standards, which could be evaluated by the Food and Drug Administration in support of a New Drug Application (NDA). The NDA for buprenorphine combined with naloxone for the treatment of opiate addiction. was filed with the FDA on June 7, 1999 by Reckitt & Colman Pharmaceuticals, Inc. The submission of the NDA represents the results of a major collaborative effort between NIH=s Medications Development Division and Reckitt & Colman. If approved by the FDA, buprenorphine combined with naloxone will be a major therapeutic advance in the treatment of opiate addiction. This product has less abuse potential than methadone, has a ceiling effect (increasing doses do not produce dose related respiratory depression) against overdose, and will generally precipitate withdrawal if injected (reducing the opportunity for HIV and hepatitis infection through needle sharing behaviors).

Implications: Buprenorphine and buprenorphine/naloxone products are expected to reach new groups of opiate addictsBfor example, those who do not have access to methadone programs, those who are reluctant to enter methadone treatment programs, and those who are unsuited to them (this would include for example, those in their first year of opiate addiction or those addicted to lower doses of opiates). If approved, these products should increase the amount of treatment capacity available and expand the range of treatment options that can be used by physicians who are treating patients who suffer from addiction.

Abstract from American Society for Clinical Pharmacology and Therapeutic Meeting, San Antonio, March 1999.

Effects of Behavioral Therapy for Cocaine Addiction Can Be Long-Lasting

Background: Significant progress has been made in the development of effective behavioral treatments for cocaine addiction. Prior studies have demonstrated that manualized treatments, treatments that have been shown to be scientifically-supported and offered with detailed guidance on how to implement the treatment in real-life practice settings, are effective. One treatment in particular, voucher-based contingency management treatment for cocaine addiction has been shown to effectively reduce cocaine abuse during outpatient treatment. This approach is an intensive behavioral treatment where patients earn points redeemable for retail items for remaining in treatment and free from cocaine. Until now researchers have not explored the long-term effects that such behavioral therapies can have.

Advance: This study provides the first demonstration that using vouchers to reinforce sustained periods of cocaine abstinence during treatment can produce sustained abstinence one year after the termination of treatment. Scientists have demonstrated that patients who received vouchers for having cocaine-free urines were more likely to have sustained cocaine abstinence during outpatient treatment than a comparative group that received incentives regardless of urinalysis results. The treatment provided to all 70 participants combined counseling based on the Community Reinforcement Approach with incentives in the form of vouchers exchangeable for retail items. In one group, incentives were delivered contingent on cocaine-free urinalysis results; while in the other group incentives were delivered independent of urinalysis results. This study provides evidence that vouchers can directly reinforce sustained cocaine abstinence during outpatient treatment for cocaine dependence.

Implications: This research not only supports previous research on this particular behavioral treatment, but includes a longer follow-up period and documents the direct role of contingent positive reinforcement in sustaining cocaine abstinence during the year after treatment. This shows the long lasting effects that behavioral treatments can have and the valuable role behavioral therapies can play in treating addictions.

Higgins et al., Contingent Reinforcement Increases Cocaine Abstinence During Outpatient Treatment and One Year Follow-up, J. of Consulting and Clinical Psychology, In Press, 1999

The Key to Addiction Treatment Success: Tailoring Treatment Approaches to Patients' Needs

Background: One of the most challenging aspects for clinicians treating addiction is determining which treatment approach is most suitable to the needs of the individual patient. A large body of research has shown that behavioral treatments work, but not every treatment works for every individual.

Advance: Research is now beginning to tell us which treatments work best for which population. A recent study evaluating the efficacy of Cognitive Behavioral Therapy (CBT) and 12-step programs in treating cocaine abuse found that the treatment outcomes varied significantly among different populations. African-American patients with strong religious beliefs appeared to benefit more from the 12-step therapy than the CBT. In a second study of patients admitted to a community-based cocaine treatment program who also had other medical, social, and psychiatric problems, researchers found that the severity of patient problems at admission was directly related to cocaine relapse in the year following discharge. Patients with moderate to high problems at admission did better in treatments that were longer in duration (90 days or longer). Both studies provide support for the importance of patient-treatment matching, since the results suggest that whether CBT or 12-step is more effective for an individual may depend on severity of problems, cultural background, and other variables.

Implications: This research suggests that when treatment approaches are matched to the specific needs of an individual they can be very effective.

Maude-Griffin PM, Hohenstein JM, Humfleet, GL, Reilly PM, Tusel DJ and Hall SM: Superior efficacy of cognitive-behavioral therapy for urban crack cocaine abusers: Main and matching effects. Journal of Consulting and Clinical Psychology, 66(5):832-837, 1998.

Simpson DD, Joe GW, Fletcher BW, Hubbard RL, Anglin MD: A national evaluation of treatment outcomes for cocaine dependence. Archives of General Psychiatry, 56:507-514, 1999.

Adolescents Who Inhale Volatile Solvents (such as glue or spray paint) Are More Prone To Delinquent Behavior

Background: The use of intoxicating inhalants by adolescents to get high, such as glue, spray paint, and lighter fluid, is a significant and increasing problem in the United States. Inhalants are particularly problematic among 8th graders, who were more likely to have tried inhalants than marijuana between 1990 and 1995. Over the years several studies have attempted to determine if there were any associations between inhalant use and delinquency. Researchers studying samples from detention facilities or drug treatment centers have in fact reported these associations, but other studies have suggested that this relationship may be deceptive, since inhalant users are more likely than nonusers to have used other drugs as well. Until now, the relationship between inhalant use and delinquent behavior had not been explored in a general population sample.

Advance: Based on a cross-sectional survey of over 13,000 students in grades 7-12 researchers found that inhalant experimenters and regular inhalant users in grades 9-12 reported more minor criminal activity than other drug experimenters and users who did not also use inhalants. Students using inhalants were more likely than those involved with other drugs to engage in some kinds of "trouble behavior," including being suspended from school, missing school due to alcohol or drug use, and getting into trouble at home because of alcohol or drug use.

Implications: The findings of this study suggest that inhalant use is more strongly associated with delinquency than is use of other drugs. One of the significant findings is that inhalant and other drug users may engage equally in minor criminal behavior in the early teenage years, but those who continue to use inhalants are more likely to continue this pattern of criminal behavior into their later adolescent years. These observations underscore the need for interventions with inhalant-abusing youth to address their criminal behavior as well as their drug use. Further study is needed to identify characteristics of inhalant users that may inform prevention interventions. [secondary B prevention]

Mackesy-Amiti ME and Fendrich M Inhalant use and delinquent behavior among adolescents: a comparison of inhalant users and other drug users. Addiction 94(4), 555-564, 1999.

Chemotherapy Plus Radiation Improves Survival of Patients With Cervical Cancer

Background: Without a doubt, our ability to prevent cervical cancer through regular Papanicolau screening testsBalso called the Pap smearBis a major public health success story in the United States. However, even with the success of the cervical cancer screening, about 15,000 women each year will learn that they have the disease, and about 4,800 women will die from it. In the developing world, cervical cancer is the second leading cause of cancer deaths among women. About 400,000 new cases are diagnosed each year, predominantly among the economically disadvantaged, in both developing and industrialized nations.

Advance: Up to now, surgery or radiation therapy alone has been considered the standard treatment for cervical cancer that has spread locally (within the cervix) or regionally (within the pelvis). Findings from five different studiesBall large, randomized clinical trialsBshow that women with cervical cancer who received both chemotherapy with cisplatin and radiation therapy, given at the same time, lived longer, with fewer disease recurrences than those treated with radiation alone. Several hundred women were enrolled in each of the five trials, which were carried out by NIH=s Clinical Trials Cooperative Groups in centers around the country. In three of the studies, women were randomly divided into groups, or Aarms@ that received either radiation alone or radiation plus concomitant chemotherapy (given at the same time as the radiation therapy). The chemotherapy agents used were cisplatin and 5-florouracil, also known as 5-FU (two studies) and cisplatin alone (one study). In all three trials, the proportion of women alive after about three years of follow-up was higher in the groups receiving chemotherapy plus radiation than in those receiving only radiation therapy. In two other studies, all patients received concomitant chemotherapy and radiation. However, the chemotherapy drugs differed between the arms. In one arm of each of these trials, the chemotherapy used was hydroxyurea while in the other arms, the chemotherapy included cisplatin. In both trials, the groups who received cisplatin had better survival rates. Although the trials vary somewhat in terms of stage of disease, dose of radiation, and schedule of cisplatin and radiation, they all demonstrate significant survival benefit for this combined approach. The risk of death from cervical cancer was decreased by 30 percent to 50 percent by concurrent chemoradiation.

Implications: The findings from these five trials are likely to change the standard of care for invasive cervical cancer. In February 1999, NIH issued a Clinical Announcement to physicians, urging them to review the data from these trials and consider using cisplatin-based chemotherapy at the same time as radiation therapy in treating women with cervical cancer.

Morris M, Eifel PJ, Lu J. et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. New England Journal of Medicine 340:1137-43, 1999.

Rose PF, Bundy BN, Watkins EB et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. New England Journal of Medicine 17:1144-53, 1999.

Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. New England Journal of Medicine 17:340:1154-61, 1999.

Thomas GM. Improved treatment for cervical cancerBconcurrent chemotherapy and radiotherapy. (editorial) New England Journal of Medicine 17:1198-1200, 1999.

Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydoxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix and negative para-aortic lymph nodes: A

Gynecologic Oncology Group and Southwest Oncology Group study. Journal of Clinical Oncology 17:1339-1348, 1999.

Eifel PJ. Concurrent chemotherapy and radiation: A major advance for women with cervical cancer (editorial). Journal of Clinical Oncology 17:1334-5, 1999.

Therapeutic Vaccine Development for B cell Lymphoma

Background: Cancer vaccines are a promising form of biological therapy currently under study. Vaccines, like other forms of biological therapy, work against cancer by creating an immune response in the body against foreign invaders (antigens). Recently, NIH researchers launched a small clinical trial to determine the effectiveness of a novel vaccine against B cell lymphoma, a common blood-cell tumor that strikes an estimated 41,000 Americans each year.

Advance: NIH researchers have developed a principle for creating therapeutic vaccines for B cell lymphoma which led to the eradication of disease in most patients in remission treated on a small phase II (efficacy) clinical trial. Vaccines were developed for each patient by obtaining the receptor molecule (tumor antigen) from the patient=s own tumor then coupling it to a carrier protein capable of creating an immune response. Then, to heighten the immune response provoked by this antigen/protein combination, a second immune system boosting substance, granulocyte colony-stimulating factors (GM-CSF) was added. GM-CSF is a substance that stimulates blood cell production and is capable of eliciting a strong T-cell responseBT cells are the white blood cells that orchestrate our immune system=s response to foreign cells. When the vaccine combination was given to the patients, the GM-CSF and carrier protein provoked an immune system attack targeted to the antigen found on the patient=s tumor. The researchers then tested each patient=s blood for the presence of remaining microscopic disease by looking for chromosomal or molecular changes only seen in cancerous cells. Of the patients analyzed, 75 percent no longer showed signs of microscopic disease.

Implication: Researchers achieved a high response rate to the B cell Lymphoma vaccine while establishing a principle for therapeutic vaccine creation that someday may be applied to more common tumors such as prostate, breast, and lung cancers.

Bendandi et al. *Nature Medicine*, in press.

An Alternative To Hospitalization For Children With Severe Mental Illness

Background: Many children suffer with a range of emotional problems, from illnesses like schizophrenia to difficulties resulting in criminal activity and other antisocial behavior. These children are managed with hospitalization or residential treatment (therapy delivered in centers away from the children=s homes), which account for most of the costs of care. However, evidence supporting the effectiveness of either hospitalization or residential treatment is lacking. Alternative treatments have been proposed, but none have been consistently shown to be as effective as hospitalization or residential careBor less expensive than either.
Researchers looked at a program known as multisystemic therapy, or AMST.@ MST uses teams who take therapy directly to the children, offering home-based care and involving families, schools, and neighborhoods in the process. Researchers looked at two pivotal questions: is MST a viable treatment for children and their families? And does it cost less to deliver?
Advance: MST, evaluated in three linked studies, offers an excellent alternative to psychiatric hospitalization or residential treatment. Researchers found that MST prevented hospitalization by more than half. For those admitted to the hospital, their stays were reduced by nearly 75%. MST was also viewed very positively by therapists, familiesBand the children themselves. And MST is less expensive to deliver, with studies of cost continuing into 2000.
MST=s success is rooted in its individualized and home-based approach. Children remain connected with their families and homes, and the families themselves are involved as helpers in the treatment goals.
Implications: After a long period of uncertainty in the psychiatric treatment community, it is now clear that children experiencing significant emotional or psychological distressBor dealing with psychiatric illnessBdo as well or better when offered an individualized, home-based treatment program. Researchers verified that hospitalization can frequently be avoided, that involved children and their families do as well or better with MST up to 4-months after treatment, and that preliminary information regarding cost suggests MST is a less-expensive alternative to hospitalization. Researchers noted that MST demands a different structure for caregiver services than are currently used in most parts of the country, but that reorganizing in support of this community-based service promises improved outcomes for children dealing with marked emotional difficulties, while reducing the financial burden of care delivery.

Henggeler SW et al.: Home-based multisystemic therapy as an alternative to the hospitalization of youths in psychiatric crisis: clinical outcomes. Journal of the American Academy of Child and Adolescent Psychiatry 38: 11, 1-9, 1999.

Rowland MD et al.: Adapting multisystemic therapy (MST) to serve youth presenting psychiatric emergencies. Child Psychology and Psychiatry Review (in press).

Schoenwald SK et al.: Multisystemic therapy (MST) vs. hospitalization for crisis stabilization of youth: placement outcomes 4 months post-referral. Mental Health Services Research (in press).

How Best To Treat Attention-Deficit/Hyperactivity Disorder (ADHD)

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a significant cause of distress and unhappiness for thousands of American children and their families. ADHD interferes with concentration and activity levels, and ADHD children have problems in school and functioning within their families. Many of these children suffer later difficulties in life and work. ADHD is a social and medical problem that demands our close and continuing attention.

Although ADHD is relatively common, our knowledge of the problem is incomplete. Current ADHD treatment includes a mix of approaches, such as drug therapy, counseling, supportive services in schools and communitiesBand various combinations of the three. The medical literature offers many studies about shorter treatment periods (three months or less), but a pressing question remains: what=s the best kind of help we can offer ADHD children over a longer term?

Advance: NIH sponsored a 14-month nationwide cooperative study, in collaboration with the Department of Education. The Multimodal Treatment Study of Children with Attention Deficit Hyperactivity DisorderBAMTA@ for shortBbrought together eighteen nationally recognized authorities in ADHD at six different university medical centers and hospitals.

Researchers divided a group of 579 ADHD children, offering them one of four different treatment plans: (1) medication alone, (2) intensive psychotherapy, (3) medication plus psychotherapy, or (4) treatment by community providers. Children who did best overall were those who received option #3Bmedication plus counseling. Reviewed from both a statistical perspective as well as how the children did in school and family life, medication plus counseling scored very well.

Implications: This is the first study to look at long-term treatment of ADHD children, filling a crucial gap in our knowledge. The MTA Study tells us that children fare better with treatment plans that include medication and intensive counseling. This study also found that medication alone is a superior option if counseling is unavailable.

The study does not claim that community-based treatment is ineffective, but rather that a carefully-designed ADHD treatment plan including medication and counseling works best. Having clear evidence of this as a result of the MTA Study, we are now able to move forward with national-level ADHD planning and treatment strategies.

Beyond that, the MTA study makes a significant step forward in our overall understanding of ADHD. The MTA conclusions offer guidance in planning the continuing education of medical professionals, and help health care administrators at all levels to design and deliver better programs for ADHD children and their families.

Jensen PS, et al: 14-month randomized clinical trial of treatment strategies for attention deficit hyperactivity disorder. Arch Gen Psychiatry (accepted for publication).

Forcing Cancer Cells to Commit Suicide

Background: Attempts to identify anti-cancer drugs that selectively target tumor cells while sparing healthy cells have been foiled by the nearly negligible differences between normal and malignant cells. But basic research into the cell cycleBthe series of precise, predetermined steps that underlie cell divisionBis providing new insights into how cell growth is regulated in both normal and malignant cells. Scientists now know that most tumor cells lack a protein "brake" that temporarily halts the cell cycle in normal cells. Lacking this brake, cancer cells proliferate unchecked and become flooded with a growth-promoting protein known as E2F.

Advance: Investigators may have discovered an Achilles heel that is unique to cancer cells and can force the cells to commit suicide. Overabundance of growth-promoting proteins such as E2F normally causes cells to self destruct, but tumor cells cleverly evade destruction by using a clean-up enzyme to sweep away excess E2F. The investigators synthesized a small peptide that can cross cell membranes and inhibit the clean-up enzyme, thereby allowing excess E2F to accumulate in cancer cells and trigger the suicide switch. Normal cells are unharmed by the inhibitory peptide, the researchers showed. Cell cycle analysis was made possible with a multi-laser, high-speed cell sorter.

Implications: Much work needs to be done to translate these basic research findings into effective drug therapies. However, discovery of the inhibitory peptides has revealed a chink in the armor of the cancer cell and has led to new windows of opportunity for drug development. Compounds similar to the inhibiting peptide are now being tested in animal models. Since the protein "brake" is deactivated in virtually all cancer cells, a therapy targeting this pathway may have wide application to a variety of tumors.

Chen YP, Sharma SK, Ramsey TM, et al.: Selective killing of transformed cells by cyclin/cyclin-dependent kinase 2 antagonists. Proceedings of the National Academy of Sciences USA 96:4325-9, 1999.

Biomolecular Underpinnings of Acute Human Leukemias

Background: Acute human leukemias are associated with chromosomal alterations of genes that encode two related proteins, the alpha and beta forms of core binding factor (CBF). CBFalpha binds to a specific region of DNA and helps regulate genes that aid blood and bone development, whereas CBFbeta complexes with CBFalpha to increase affinity for the DNA binding sites. The structural details of the interactions between the two CBF proteins and DNA are poorly understood.

Advances: Using advanced nuclear magnetic resonance instruments, scientists at Rockefeller University analyzed the three-dimensional structures of CBFalpha and CBFbeta proteins and identified the specific portion of CBFalpha that interacts with DNA. The researchers also found evidence that CBFbeta does not directly associate with DNA but rather stabilizes the DNA-binding surface of CBFalpha, facilitating its interactions with DNA.

Implications: These studies reveal how structural abnormalities in the CBF proteins might prevent or inhibit binding to DNA, and thereby interfere with regulation of blood and bone development. Because abnormalities in CBF proteins have been implicated as contributors to acute human leukemias and other developmental disorders, studying the structure and functions of these molecules can lead to new insights into leukemogenesis and related chromosomal/genetic anomalies. Many of these genetic alterations have important prognostic implications that can guide the selection of therapy. The insights gained from studies of translocation-generated oncogenes and their protein products should hasten the development of highly specific, and hence less toxic, forms of leukemia therapy.

Nagata T, Gupta V, Sorce D, Kim W-Y, Sali A, Chait BT, Shigesada K, Ito Y, and Werner MH: Immunoglobulin motif DNA recognition and heterodimerization of the PEBP2/CBF Runt domain. Nature Structural Biology 6:615-9, 1999.

Transplants Save Lives of Children with Severe Immune Disorders

Background: Children born with severe combined immunodeficiency (SCID), a rare syndrome marked by a profound shortage of immune system cells, often die from common infections within the first year of life. Bone marrow transplantation has been used for more than 30 years to help reconstitute the immune systems of patients, allowing hundreds to survive for several years or even into their teens. However, reliable data on the long-term efficacy of this treatment are limited.

Advance: By analyzing the outcomes of 89 patients with SCID who had received bone marrow transplantations, scientists working at Duke University discovered that the treatment is most successful when patients receive a family member's bone marrow within the first 3.5 months of life; all but 1 of 22 babies who received such treatment survived. Of the 89 children studied, including those diagnosed well after the first months of life, more than 70 are still alive and faring well for as long as 16 years after transplantation. The researchers also determined that parents as well as siblings of SCID-affected babies can be successful marrow donors, as long as mature immune cells known as T cells are removed from the donor bone marrow before transplantation. Removing mature immune cells prevents their attacking the patient's vital organsBa serious complication of transplantation known as graft-versus-host disease.

Implications: Once considered an incurable, fatal condition, SCID can now be considered a pediatric emergency that is curable with early diagnosis and treatment. If newborn screening can detect the genetic defect, babies with SCID might receive a life-saving transplant from either a sibling or a parent within the first few days of life.

Buckley RH, Schiff SE, Schiff RI, Markert ML, Williams LW, Roberts JL, et al.: Hematopoietic stem cell transplantation for the treatment of severe combined immunodeficiency. New England Journal of Medicine 340:508-16, 1999.

Leishmaniasis: New Insights into Factors Responsible for Disease Severity

*Background***:** Leishmaniasis is a common tropical parasitic disease that results in ulcers of the mucous membranes and destruction of the soft tissues of the nose and throat or internal organs. There are no vaccines and few effective treatments. The severity of the disease appears to depend on the extent of body=s immune reaction to the presence of the parasite. In some cases the body's immune response cures the infection and in others the response increases the severity of the disease. The purpose of this study was to compare the body=s early and long-term immune responses to leishmaniasis, and to show how the response can become misdirected to cause a long-term, more severe disease.

Advance: Numerous aspects of immune response were measured over time in patients with early signs of leishmaniasis and compared to measurements from patients with long term infections. This study showed that some patients with an early infection show a transitory depression of the Th1 type of immune response that can proceed to cure the disease if it rebounds. Patients with long term severe leishmaniasis lack the Th1 immune response and instead generate an ineffective Th2 immune response. These changes were then shown to be reversible. Scientists treated the patient's immune cells in a test tube with either IL-12 that mediates the Th1 response, or with a neutralizing antibody (IL-10) which mediates the Th2 immune response. Both treatments restored Th1 function of the immune cells. These results demonstrate that when an immune response that could potentially cure people is misdirected, leishmaniasis infection may progress to a longer term, more severe disease. It is however possible to reverse this change so that an effective immune response, which cures the infection, can be restored.

Implications: These results suggest that an alternate strategy may be more effective in treating leishmaniasis. It may be better to develop drugs or vaccines, which directly affect the immune response instead of trying to kill the parasite. A vaccine or drug that could either maintain the early immune response to the infection *o*r reverse the later misguided immune response might cure leishmaniasis before significant damage to the body occurs.

Rocha PN, Almeida RP, Bacellar O, de Jesus AR, Filho DC, Barral A, Coffman RL and Carvalho EM: Down-Regulation of Th1 Type of Response in Early Human American Cutaneous Leishmaniasis. Journal of Infectious Diseases. In Press, 1999

A Combination of Anti-Retroviral Therapy and Interleukin-2 has Potential to Eliminate the Reservoir of HIV in Resting T Cells

Background: Highly active anti-retroviral therapy (HAART) has driven the level of HIV in plasma to below the levels of detectability in a substantial portion of HIV-infected individuals. Despite this success, the persistence of a latent reservoir of HIV in a particular immune cell type (resting CD4+ T cells) in HAART-treated individuals is a major impediment to the long-term control of HIV infection. This is so because the virus often rebounds, presumably from this reservoir of long lived cells, when HAART is discontinued, even after several years of treatment. In an effort to diminish or eliminate latently infected resting CD4+ T cells in HIV infected individuals receiving HAART, scientists investigated the use of an immune-modulator, interleukin-2 (IL-2), to purge the latent HIV in resting CD4+ T cells. They hypothesized that IL-2 could induce resting latently infected cells to become active and that, once active, the cells would become targets for the cell-killing (cytopathic) effects of the virus and/or immune effector mechanisms. At the same time, the HAART therapy would prevent new rounds of infection resulting from the virus produced by the newly active infective cells before those cells are killed off.

Advance: A non-randomized, cross-sectional analysis of resting CD4+T cells was done in small groups of HIV-1 infected patients receiving intermittent IL-2 plus continuous HAART, or receiving continuous HAART alone. The frequency of resting CD4+ T cells carrying infectious (replication-competent) HIV in the blood of patients receiving IL-2 plus HAART was significantly lower than that of patients receiving HAART alone. Infectious HIV was not detected by standard co-culture assays in six of 14 patients receiving IL-2 plus HAART, whereas all 12 patients receiving HAART alone carried infectious HIV in their resting CD4+ T cells. The six patients receiving IL-2 plus HAART, who did not have virus by standard assays, were studied more intensively. It was shown that virus could not be isolated from the peripheral blood CD4+ T cells in three of them even when large numbers of resting CD4+ T cells were cultured. Lymph node biopsies were then performed in two of these three patients and virus still could not be isolated.

Implications: The investigators noted that this study does not prove that HIV was eradicated. However, the results suggest that the intermittent administration of IL-2, together with continuous HAART, may lead to a substantial reduction in the pool of resting CD4+ T cells that harbor replication-competent HIV. Further randomized studies on larger numbers of patients are needed to fully assess the effect of the HAART plus IL-2 regimen.

Chun TW, Engel D, Mizell SB, Hallahan CW, Fischette M, Park S, Davey Jr., RT, Dybul M, Kovacs JA, Metcalf JA, Mican JM, Berrey MM, Corey L, Lane HC, & Fauci, A.S: Effect of interleukin-2 on the pool of latently infected, resting CD4+ T cells in HIV-1-infected patients receiving highly active anti-retroviral therapy. Nature Medicine 5(6): 651-655, 1999.

Controlling Acquired Chemoresistance of Tumors by Inhibition of NF-κB

Background: A major problem in the treatment of cancers is acquired resistance of tumors to chemotherapy or radiation therapy. Increasing the concentrations of cytotoxic drugs or the dose of radiation is generally ineffective in enhancing anti-tumor responses. This has stimulated research efforts directed toward definition of the mechanisms by which tumors become resistant and potential means for overcoming these barriers to effective treatment.

Advance: It now appears that programmed cell death (apoptosis) is a principal mechanism behind the beneficial effects of such treatments as chemotherapy and radiation. Resistance to apoptosis allows tumors to evade these therapies. The protein called nuclear factor-kappa B or NF-κB is activated by chemotherapy and by irradiation in some cancer cell lines. Activation of NF-κB markedly suppresses apoptosis. Conversely, inhibition of NF-κB *in vitro* can lead to enhanced apoptosis. *In vitro* and *in vivo* studies using gene therapy to deliver an inhibitor of NF-κB to tumor cells or to tumors transplanted into mice have demonstrated inhibition of NF-κB. This inhibition made chemoresistant tumor cells susceptible to the apoptotic effects of both tumor necrosis factor alpha (TNFα) and the chemotherapeutic agent CPT-11, resulting in tumor shrinkage, and in some cases complete eradication. These studies clearly demonstrate that the activation of NF-κB in response to therapy is a principal mechanism of inducible tumor resistance which may be overcome by NF-κB inhibiton.

Implications: Of major significance are the findings that inhibition of NF-κB in conjunction with the administration of biological factors, such as TNFα, or chemotherapeutic agents such as CPT-11, may provide a powerful new approach to therapy in cancer treatment.

Wang C-Y, Cusack JC, Liu R, and Baldwin, AS. Control of inducible chemoresistance: Enhanced anti-tumor therapy through increased apoptosis by inhibition of NF-kB. Nature Medicine 5: 412-17, 1999.

Dietary Supplement Stimulates Muscle Regeneration after Traumatic Injury

Background: Skeletal muscles (muscles under voluntary control) are common sites of traumatic or surgical injury and disease. Until recently, there have been no effective treatments to stimulate repair of damaged muscles. Progress in cell biology revealed the existence of substances called growth factors that enhance cell growth in various body tissues. However, direct application of these substances to injured muscle tissue has shown only limited success in producing repair. An ideal substance for treating muscle injuries would be effective when given systemically, rather than requiring direct application into the injured muscle. Such an approach would be particularly effective in situations of diffuse muscle injuries.

Advance: Curcumin, a substance derived from the same plant as the spice cumin, has been shown to possess anti-inflammatory properties, and was recently shown to enhance the healing of skin wounds. Scientists have now shown that systemically administered curcumin enhances the repair of traumatized skeletal muscles in animals. The data suggest that curcumin stimulates muscle cell division or growth, as well as enhancing the development of newly formed muscle cells into mature muscle fibers. Curcumin is the first example of a substance that appears to have the ability, when given systemically, to stimulate the repair of damaged skeletal muscles.

Implications: Learning the precise mechanism of action of curcumin may allow the development of orally active derivatives with enhanced muscle regenerating ability. This discovery holds the promise of developing a new class of drugs to enhance the repair of skeletal muscles damaged by trauma, reconstructive surgery, or sports-related injuries. Such research may also shed light on the mechanism(s) of the other known biological actions of curcumin. [secondary B prevention]

Thaloor D, Miller KJ, Gephart J, Mitchell PO, and Pavlath GK: Systemic administration of the NF-kB inhibitor curcumin stimulates muscle regeneration after traumatic injury. Amer J Physiol (Cell Biol) 277 (2): C320-29.

Tissue Engineering and Neo-Organ Formation

Background: Photopolymerization, uses light to polymerize or cure biomaterials used for such applications as bone repairs, dental restorations and coatings of artificial implants. It requires shining light directly on polymers to initiate a photopolymerization either in accessible locations such as the oral cavity or during invasive surgical procedures. NIH-funded investigators hypothesized that light could penetrate skin tissue and cause indirect photopolymerization of liquid biomaterials injected subcutaneously. Transdermal photopolymerization could effectively allow implantation of biomaterials for plastic surgery, including both biodegradable and nondegrading polymers, and potentially enable cells or drugs to be injected and encapsulated for tissue engineering, drug delivery or other applications.

Advance: A liquid polymer containing cartilage cells (chondrocytes) was injected subcutaneously into mice and then exposed to ultraviolet light shined through the skin for three minutes. The transdermal light exposure did result in photopolymerization of the injected material. After two or more weeks, the implanted material was removed and found to contain tissue typical of neocartilage. These results are promising for future tissue engineering applications of transdermal photopolymerization.

Implications: This approach is a step forward in developing strategies for tissue engineering of "neo-organs" that can be used to treat patients with vital organ malfunction due to trauma, disease and/or genetic defects. Such technologies have potential for application in treatment of sports injuries, severe forms of arthritis, and disorders of the temporomandibular (jaw) joint. [secondary B technologies]

Elisseeff J, Anseth K, Sims D, McIntosh W, Randolph M, and Langer R: Transdermal photopolymerization for minimally invasive implantation. Proc Natl Acad Sci USA 96: 3104-107, 1999.

SCIENCE CAPSULES

Testosterone Supplements in Older Men. Circulating levels of testosterone are known to decline in older men as they age, leading to bone loss. A recent clinical trial of testosterone supplementation in a group of older men with low natural hormone levels revealed very little difference in bone mineral density between the placebo- or testosterone-treated men when the groups were compared as a whole. Only men with the lowest initial testosterone levels increased their bone density by 5 percent, indicating that hormone therapy to replace bone mass is not necessary for most older men.

Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh, L, Holmes JH, Diewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad JG, Strom BL: Effect of Testosterone Treatment on Bone Mineral Density in Men Over 65, J Clin Endo Met, in press.)

Promoting Tolerance to Ischemia in Stroke. Most strokes are caused by ischemia, a severe block of the blood supply to the brain. Ischemia sets in motion a cascade of harmful processes that ultimately can kill brain cells and cause serious disability. Researchers have known for some time that a less severe episode of ischemia increases the tolerance of brain cells to a subsequent more serious disruption of blood flow, but this tolerance requires 24-48 hours to developCtoo long to be useful in protecting against acute stroke. Now scientists have found a chemical signal that is part of the sequence of steps by which brain cells develop tolerance after mild ischemia. This chemical, ceramide, can rapidly induce tolerance in cell culture and animal models of stroke and presents a new strategy to reduce the damage caused by stroke.

Ginis I, Schweizer U, Brenner M, Liu J, Azzam N, Spatz M, and Hallenbeck JM: TNF-alpha pretreatment prevents subsequent activation of cultured brain cells with TNF-alpha and hypoxia via ceramide. Am J Physiol 276:C1171-83, 1999.

Liu J, Spatz M, and Hallenbeck JM: Hypoxic preconditioning protects cultured nerve cells against hypoxic stresss via TNF-alpha and ceramide. Am J. Physiol. *in press*

Embryonic Stem Cells in Animal Models of Cell Therapy. Embryonic stem cells may provide a virtually unlimited supply of donor cells for transplantation if scientists can learn how to coax these cells to multiply and to specialize to become the required cell types. A new study demonstrates that rat embryonic stem cells placed in certain cell culture conditions will respond to a controlled combination of natural growth factors to produce supporting cells of the nervous system that produce myelin, the essential electrical insulation of nerve cell fibers. When these cells were transplanted into rats with the same myelin-deficiency that causes human Pelizaeus-Merzbacher disease, the cells efficiently interacted with the animals nerve cells and repaired the myelin deficiency. This encourages hope that embryonic stem cells will someday be a source of replacement cells to treat many diseases of the nervous system.

Brustle O, Jones KN, Learish RD, Rarram K, Choudhzary K, Wiestler OD, Duncan ID, McKay RDG: Embryonic stem cell-derived glial precursors: a source of myelinating transplants. Science 285: 754-56, 1999.

Successful Gene Therapy in an Animal Model of Muscular Dystrophy. Several forms of muscular dystrophy are caused by inherited defects in muscle proteins that cause structural defects in the muscle membrane and lead to muscle loss. Previous attempts to replace the missing proteins have been unsuccessful because of the difficulty of repairing the millions of muscle cells of the body. Now, researchers have successfully replaced a missing protein, called delta-sarcoglycan, in hamsters that share the same muscle defect as people with a type of limb girdle muscular dystrophy (LGMD). The scientists inserted the gene for sarcoglycan into millions of copies of a virus that had been rendered harmless but retained the capacity to infect muscle cells. They injected the viral particles into the blood supply to a limb and used histamine, a natural regulator, to trick the blood vessels into becoming temporarily leaky enough to allow the viruses to pass through to the muscle cells. This procedure efficiently protected muscle fibers from degeneration. The researchers are now adapting their procedure for human clinical trials.

Greelish JP, et al: The restoration of the sarcoglycan complex in dystrophic muscle perfused with histamine and a recombinant adeno-associated viral vector. Nature Medicine 5:439-43, 1999.

Improved Treatment for Late Stage Parkinson=s Disease. Research indicates that an inexpensive and commonly available drug used to treat early Parkinson=s disease can bring previously unsuspected benefits to those at more advanced stages of the disorder. The new studies found that drugs targeted to block certain types of nerve cell receptors for the neurotransmitter glutamate (called NMDA receptors) can provide dramatic relief from the complications that eventually disable Parkinson=s patients.

Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J, Mouradian MM, and Chase TN: Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson=s disease. Neurology 50: 1323-1326, 1998.

Epidemiology of Diabetes Interventions and Complications (EDIC). Using a standardized annual history and physical examination, 28 EDIC clinical centers that were DCCT clinics are following the EDIC cohort for 10 years. Annual evaluation also includes a resting electrocardiogram, ultrasound (Doppler) measurements of ankle/arm blood pressure, screening for kidney damage (nephropathy). At regular intervals, a timed 4-hour urine is collected, lipid profiles are obtained, and stereoscopic fundus photographs are taken. In addition, ultrasound scans of the common and internal carotid arteries are performed at years 1 and 6 and at study end. The results to date show that the participants, compared with nonparticipants, tended to have better blood sugar (glycemic) control at the completion of the DCCT and were more likely to have their diabetes care provided by DCCT personnel. The EDIC baseline measurement stratified by sex delineates multiple cardiovascular disease risk factor differences such as age (older in men), waist-to-hip ratio (higher in men), high density lipoprotein (HDL) cholesterol (lower in men), hypertension (more prevalent in men), and maximum thickness of common and internal carotid arteries (thicker in men). Of the original conventional treatment group, 69% have changed to continuous subcutaneous insulin infusion or multiple daily injections. Although the mean difference in blood sugar level (measured by hemoglobin A1c level) between the intensive and conventional treatment groups narrowed at EDIC years 1 and 2, Hemoglobin A1c remained

significantly lower in the intensive group. Of all expected clinic visits, 95% were completed, and the quality of EDIC data is very similar to that observed in the DCCT.

Design, implementation, and preliminary results of a long-term follow- up of the Diabetes Control and Complications Trial (DCCT) cohort. Diabetes Care 1999;22:99-111.

Simultaneous Pancreas-Kidney Transplantation: Mortality in Type 1 Diabetes and End-Stage Kidney Failure. The long-term prognosis of patients with type-1 diabetes mellitus and end-stage renal failure appears to be better after kidney transplantation compared with dialysis. Controversy exists about the additional benefit of a simultaneously transplanted pancreatic graft. This study looked at the effect on mortality of simultaneous pancreas-kidney transplantation compared with kidney transplantation alone from regional differences in transplantation protocols. All 415 patients with type-1 diabetes (aged 18-52 years) who started renal-replacement therapy in the Netherlands between 1985 and 1996 were included in the analysis. Patients were allocated to a center based on their place of residence at onset of renal failure. In the Leiden area, the primary treatment approach was with simultaneous pancreas-kidney transplantation, whereas in the non-Leiden area, kidney transplantation alone was the predominant type of treatment. All patients were followed up to July, 1997. The risk (hazard ratio) for mortality was significantly lower in the Leiden area compared with the non-Leiden area for transplant patients, although equal survival was found for patients on dialysis only. These data support the hypothesis that simultaneous pancreas-kidney transplantation prolongs survival in patients with diabetes and end-stage renal failure.

Smets YF et al., *Effect of simultaneous pancreas-kidney transplantation on mortality of patients with type-1 diabetes mellitus and end-stage renal failure.* Lancet 1999;353:1915-9

Aminoglycoside-Induced Ototoxicity. Aminoglycoside antibiotics are used to treat several serious infections caused by gram negative bacilli, including pneumonia and multi-drug resistant tuberculosis. These antibiotics have a rapid onset of action, a low rate of resistance, synergy with other antibiotics, and a low cost. Unfortunately, the use of these antibiotics is severely limited due to the risk of inducing toxicity to the ear (ototoxicity) that may result in permanent hearing impairment or hearing loss. As aminoglycosides can act as activators of protein molecules that recognize and bind a particular toxic agent (receptors for N-methyl-D-aspartate, or NMDA), NIH researchers are studying the role of NMDA receptor inhibitors in aminoglycoside-induced ototoxicity. Using the guinea pig as a model, researchers found that co-administration of NMDA inhibitors with ototoxic regimens of aminoglycoside antibiotics significantly attenuated both the hearing loss and the sensory hair cell destruction that are characteristic of ototoxicity. If the ototoxic effects of aminoglycosides are produced through the activation of NMDA receptors, then appropriate regimens of NMDA inhibitors co-administered with the antibiotics should completely block ototoxicity, increasing both the usefulness and safety of this important class of antibiotics.

Dizocilpine Attenuates Streptomycin-Induced Vestibulotoxicity in Rats. Basile AS. Neuroscience Letters 1999; 265(2):71-74.

Old Cancer Therapy May Have New Life. Before the advent of modern chemotherapy and radiation therapy for cancer treatment a number of modalities were employed with varying results. One was based on immunotherapyBthe stimulation of the immune system to protect the body and bolster the natural healing response. A turn-of-the-century surgeon, William B. Coley, pioneered immunotherapy. He observed that sarcoma patients who developed streptococcal infections postoperatively fared better than patients who remained free of infection. Accordingly, Dr. Coley formulated a therapy containing two strains of heat-killed bacteria that became known as Coley toxins. He used this therapy to treat hundreds of cancer patients from 1891 through 1936. Recently, a cohort of Dr. Coley's patients was retrospectively evaluated for survival compared to patients diagnosed in 1983 and treated with nonradiotherapeutic conventional approaches. The absence of an increased mortality, especially in light of advances in surgical techniques, and medicine in general, suggest that the old therapy may merit a reevaluation.

Richardson MA, et al.: Coley Toxins Immunotherapy: A Retrospective Review. Alternative Therapies 5:3: 42-47, 1999.

Yoga Techniques Show Promise for OCD. Obsessive Compulsive Disorder (OCD) is a life-long and disabling psychiatric condition. It is proven to be refractory to traditional insight-oriented psychotherapy and only modestly improved by pharmacological management and behavioral therapy. In placebo-controlled studies of OCD, researchers have used Kundalini Yoga techniques and observed encouraging improvements as measured by behavioral diagnostic indices. Kundalini Yoga provides an alternative to conventional medical approaches for the treatment of OCD and warrants further study.

Shannakoff-Khalsa, BS, et al.: CNS Spectrums. Intl J Neuropsychiatric Med in press, 1999.

Ocular Estrogen Receptor Discovered. Gender-based differences in the incidence of several important ocular conditions raise the possibility that estrogens may have direct effects on the human eye. Scientists using immunochemical techniques recently detected estrogen receptor protein in the retina and retinal pigment epithelium of young females, but not in eye tissues of men or postmenopausal women. This hormone receptor may offer a new therapeutic target for the treatment of dry eye syndromes.

Ogueta SB, Schwartz SD, Yamashita CK and Farber DB: Estrogen receptor in the human eye: influence of gender and age on gene expression. Invest Ophthalmol Vis Sci 40(9): 1906-1911, 1999.

Drug Inhibits Growth of New Blood Vessels in the Eye. A new therapeutic agent has been developed that may be important in preventing vision loss in humans from diabetic retinopathy or macular degeneration. Vessels that grow abnormally in the eyes can leak fluid or blood, causing rapid and severe vision loss. The new drug, called PKC 412, can be taken orally and appears to have several actions on growth factors and their receptors within the retina. While

PKC 412 blocks new abnormal vessel growth, it has no apparent adverse effects on normal, fully mature vessels.

Seo MS, Kwak N, Ozaki H, Yamada H, Fabbro D, Hofmann F and Campochiaro PA: Dramatic inhibition of retinal and choroidal neovascularization by oral administration of a kinase inhibitor. Am J Path 154(6):1743-1753, 1999.

New Help for Patients with Congenital Nystagmus. Congenital nystagmus is a condition that begins at birth or early infancy where the eyes oscillate continuously and uncontrollably. This condition can be familial, but more commonly it is associated with many diseases of the visual system that also begin in infancy. Treatment of this condition is usually aimed at associated problems, e.g., strabismus, anomalous head posturing, refractive error correction, and amblyopia treatment. It has been recently discovered in an animal model of this condition that surgical cutting of the extraocular muscle tendons (endotomy) decreased the nystagmus and improved the visual behavior. This procedure has entered a phase I study in humans with the hope of decreasing their nystagmus and improving the visual function of patients with this condition.

Dell-Osso LF, Hertle RW, et al: A new surgery for congenital nystagmus: effects of tenotomy on an achiasmatic canine and the role of extraocular muscle proprioception. J Am Assn Ped Ophthalmol Strab 3:166-182, 1999.

Mechanisms Involved in Modulation of Uveitis through feeding of Retinal Proteins. Feeding of retinal proteins to animals protects them from developing autoimmune retinal disease after a subsequent immunization with the same proteins, a phenomenon known as oral tolerance. Clinical studies have also suggested that a similar phenomenon may operate in humans. Recently, scientists studied the involvement in this process of soluble factors, known as cytokines, that are produced by lymphoid cells and regulate their function. Studies with mice that were genetically engineered to lack particular cytokines indicated that two anti-inflammatory cytokines, known as interleukin 4 and interleukin 10, are involved in this process. This suggests that augmentation of these cytokines may be a useful approach to potentiating oral tolerance in a therapeutic setting.

Rizzo LV, Morawetz RA, Miller-Rivero NE, Choi R, Wiggert B, Chan CC, Morse HC, Nussenblatt RB, and Caspi RR: IL-4 and IL-10 are both required for the induction of oral tolerance. J Immunol 162: 2613-2622, 1999.

Head and Neck Cancer. Cancer of the head and neck account for tens of thousands of deaths each year in the United States. Current therapeutic regimens often leave patients with many problems, including difficulties is swallowing and speaking. NIH intramural scientists have recently completed a successful Phase 1 clinical trial where patients with advanced head and neck cancer are treated with a combination of Paclitaxel and radiation, and sixty percent of patients enrolled achieved a complete remission.

Thomas GR, Chen Z, Oechsli MN, Hendler FJ and Van Waes C: Decreased expression of CD80 is a marker for increased tumorigenicity in a new murine model of oral squamous-cell carcinoma. Int J Cancer 82(3): 377-84, 1999.

Mouse Model May Lead To Treatment of a Common Human Kidney Disorder. Researchers at NIH and the Baylor College of Medicine have uncovered a major clue to the possible cause and treatment of Immunoglobin A nephropathy, a kidney disorder that affects hundreds of millions of people throughout the world. The researchers induced the disease in mice by stopping the gene for a substance known as uteroglobin from functioning, then prevented the disease by treating the mice with uteroglobin. Although treatments that are successful in animal Amodels@ of human disease need to be confirmed in human beings, the finding offers very specific strategies for possibly determining the cause of the human condition and ultimately designing a treatment for it.

Zheng F, Kundu GC, Zhang Z, Ward J, DeMayo F, and Mukherjee AB: Uteroglobin is essential in preventing immunoglobin a nephropathy in mice. Nature Medicine 5: 1-7, 1999.

Early Revascularization Brings Late Rewards. Early intervention to restore circulation in patients with acute heart failure following a heart attack has been shown to offer a clear survival advantage in a recently reported clinical trial. Despite a wide range of treatment improvements for patients suffering a heart attack, the high mortality rates (up to 80 percent) have remained unchanged for those patients who also experience acute heart failure. Although no mortality advantage was apparent 30 days after onset in patients who received early revascularization, either by coronary artery bypass surgery or angioplasty, as compared with the medical treatment group, after six months 63 percent of the revascularization group survived as compared with 50 percent of the medical treatment group.

Hochman JS, Sleeper LA, Webb JG et al: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. NEJM 341:625-634, 1999.

New Hope for Hemophilia B Cure. Recent research offers the possibility for enabling patients with hemophilia B to produce the clotting protein, factor IX, that they lack and thereby cure them. Dogs with hemophilia B that were injected or infused with the normal canine form of the gene for factor IX have shown sustained production of factor IX for up to 23 months and partial correction of whole-blood clotting time with only transient or no side effects. The agent used to treat the dogs, an adeno-associated virus engineered to carry the gene that produces factor IX, is under consideration by the Food and Drug Administration for human trials.

Herzog RW, Yang EY, Couto LB et al: long-term correction of canine hemophilia b by gene transfer of blood coagulation factor IX mediated by adeno-associated viral vector. Nature Medicine 5:56-63, 1999.

Snyder RO, Miao C, Meuse L et al: Correction of hemophilia B in canine and murine models using recombinant adeno-associated viral vectors. Nature Medicine 5:64-70, 1999.

Inhaled Antibiotics Benefit Cystic Fibrosis Patients. Intermittent administration of an inhaled antibiotic has recently been shown in two clinical trials to be effective in controlling the bacterial infections of the lung that plague patients with cystic fibrosis (CF). Although intravenous

administrations of antibiotics have been effective in treating periodic lung infections in CF patients, affected patients typically experience a continued decline in pulmonary function and many of them ultimately die of lung disease. However, patients in the trials, who had both CF and a particular bacterial infection and received the inhaled antibiotics, not only showed lower levels of infection with the bacteria, but also maintained their level of lung function and experienced fewer hospitalizations. Lung function is the best predictor of morbidity and mortality in CF patients, and hospitalizations are a direct measure of morbidity, so the lung function benefits and reduced hospitalizations found in the trial offer hope for longer, healthier lives for CF patients.

Ransey BW, Pepe MS, Quan JM et al: Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. NEJM 340:23-30, 1999.

Safe Treatment for Children With Sickle Cell Disease. A recent finding that the chemotherapeutic drug hydroxyurea can safely be used to treat adults with sickle cell disease has now been extended to children between the ages of 5 and 15 years. A clinical trial demonstrated that the drug induced significant elevations in levels of both total and fetal hemoglobin (which is believed to prevent the characteristic Asickling@ of red blood cells) without any adverse effects on growth and development. This new approach to relieving symptoms in severely affected children has the potential to improve quality of life and decrease health care costs significantly.

Kinney TR, Helms RW, O=Branski, EE et al: Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Blood 94:1550-1554, 1999.

Reducing Cocaine Craving in Animals. Researchers have developed a compound, BP 897, that appears to reduce cocaine Acraving@ in animals. The selective partial agonist BP 897 works on the D3 receptor, one of the known dopamine receptors found on the surface of brain cells, that is thought to be involved in the reinforcing effects of cocaine. The compound was found to reduce cocaine-seeking behavior in rats trained to associate cocaine taking with a light. The light represents an environmental cue or stimulus, which the rat learns to associate with cocaine administration, the same way that the mere sight of drug paraphernalia can trigger craving in human cocaine addicts who have been abstinent for years. The compound was found to block the cued response, thus bringing us at least one step closer to having a medication for cocaine addiction.

Pilla M, Perachon S, Sautel F, Garrido F, Mann A, Wermouth CG, Schwartz JC, Everitt BJ, and Sokoloff P. Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 receptor agonist. Nature: Volume 400, 22 July 1999. 371-375.

The Nicotine Antagonist, Mecamylamine, Decreases Cocaine Craving in Crack Users. Use of the nicotine patch has been shown to enhance environmentally induced cocaine craving in crack abusers who also smoke. In a recent study, scientists have found that the nicotine antagonist, mecamylamine can actually decrease the craving for cocaine triggered by

environment cues associated with its use. These results suggest that mecamylamine may be a valuable aid in relapse prevention among cocaine abusers.

Reid MS, Mickalian JD, Delucchi KL, and Berger P. A nicotine antagonist, mecamylamine, reduces cue-induced cocaine craving in cocaine-dependent subjects. Neuropsychopharmacology 20:297-307, 1999.

Major Depression and Attention -Deficit/hyperactivity Disorder Increase the Severity of Nicotine Addiction. Attention-deficit/hyperactivity disorder and major depression significantly contribute to the severity as well as an earlier onset of nicotine dependence in juvenile delinquents. The findings highlight the need for conducting comprehensive clinical assessments and selecting smoking treatment strategies that simultaneously consider co-occurring mental disorders and use of other illicit drugs when planning treatment for these multi-problem youths.

Riggs PD, Mikulich SK, Whitmore EA, Crowley TJ. Relationship of ADHD, depression, and non-tobacco substance use disorders to nicotine dependence in substance-dependent delinquents. Drug and Alcohol Dependence 54: 195-205, 1999.

Predicting the Success or Failure of Treatment for Drug Addiction. A new study suggests that clinicians can predict who is at greatest risk for dropout within two weeks of entry into a methadone treatment program. Individuals who enter early counseling sessions and did not have any incidents of drug use during the first two weeks of entering the program were most likely to remain abstinent up to 9 months later. By identifying early on in the treatment process those individuals who are likely to succeed or fail, clinicians will be able to better tailor treatment programs to match the patient=s needs.

Morral AR, Belding MA, Iguchi MY. Identifying methadone maintenance clients at risk for poor treatment response: pretreatment and early progress indicators. Drug and Alcohol Dependence 55: 25-33, 1999.

Acupuncture: A Treatment for Cocaine Addiction? A recent study has attempted to rigorously evaluate the effectiveness of acupuncture as a treatment adjunct for cocaine addiction using a randomized, placebo controlled study. Using this approach, scientists determined that acupuncture did not significantly improve treatment outcome.

Bullock ML, Kiresuk TJ, Pheley AM, Culliton PD, and Lenz SK. Auricular acupuncture in the treatment of cocaine abuse. Journal of Substance Abuse Treatment 16: 31-38, 1998.

Treatment of Leukemias and Lymphomas with the Immunotoxin LMB-2. Immunotoxins are specialized molecules that consist of two components: a protein that targets tumor cells, and a poison, or toxin, that is then delivered directly to the cancer cell, killing it. In a Phase I clinical trial (a study to determine the safety of a new treatment) of the recombinant immunotoxin LMB-2, 40 percent of participating patients with leukemia, lymphoma, and Hodgkin's disease had major responses to the drug, and the treatment was well tolerated. LMB-2 is a single-chain

protein, with one part containing a region that binds to the protein CD25, found on the surface of malignant cells, and the other part containing a powerful toxin derived from the bacteria Pseudomonas. LMB-2 binds to CD25 on the surface of the malignant cells in patients, enters the cell, and then kills the cell with the toxin. A Phase I trial for a new recombinant immunotoxin, BL22, whose mechanism is similar to that of LMB-2, is currently under way in patients with B-cell leukemias and lymphomas, and early results are extremely promising, especially among patients with chronic lymphocytic leukemia and hairy cell leukemia.

Kreitman RJ, Wang Q-C, FitzGerald DJP, and Pastan R: Complete regression of human B-cell lymphoma xenografts in mice treated with recombinant anti-CD22 immunotoxin RFB4 (dsFv)-PE38 at doses tolerated by cynomolgus monkeys. International Journal of Cancer 81: 148-155, 1999.

Kreitman RJ, Wilson WH, Robbins D, Margulies I, et al.: Responses in refractory hairy cell leukemia to a recombinant immunotoxin. Blood, in press.

The Development of Cancer Vaccines. The development of vaccines for the treatment of patients with cancer is dependent on the molecular identification of the antigens, present on the surface of cancer cells, that are recognized by the immune system. Researchers have cloned the genes encoding over 10 different tumor antigens present on malignant melanomas and have characterized the proteins and immunodominant peptides (amino acid compounds) from these antigens. In addition, NIH has recently completed a pilot trial in which patients with metastatic melanoma were immunized with an immunodominant peptide and the drug interleukin-2; 42 percent of the patients responded to this new treatment.

Rosenberg SA, Yang JC, Schwartzentruber DJ, et al.: Immunologic and therapeutic evaluation of a synthetic peptide vaccine for the treatment of patients with metastatic melanoma. Nature Medicine 4: 321-327, 1998.

Rosenberg SA.: A new era for cancer immunotherapy based on the genes that encode cancer antigens. Immunity 10: 281-287, 1999.

Prostate Cancer Treatment. 3-Dimensional Conformal Radiation Therapy (3DCRT) is a new approach that employs sophisticated computer technology to focus the treatment field more tightly to the tumor, in three dimensions, than was possible using conventional techniques. In a Phase I study, researchers used 3DCRT for treatment of patients with advanced prostate cancer. In comparison with standard treatments, they found that they can safely give higher doses of radiation to the tumor and increase the probability of local tumor control. An advanced form of 3DCRT, Intensity-Modulated Radiotherapy, which uses non-uniform radiation beams for further improvement in dose distribution, was further found to significantly reduce the probability of both acute and delayed rectal complications.

Zelefsky MJ, Fuks Z, Happersett L, et al.: Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiotherapy and Oncology, in press.

Zelefsky MJ, Fuks Z, Wolfe T, et al.: Locally advanced prostatic cancer: Long-term toxicity outcome after three-dimensional conformal radiation therapy B a dose-escalation study. Radiology 209: 169-174, 1998.

Zelefsky MJ, Leibel SA, Gaudin PB, et al.: Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. International Journal of Radiation Oncology 41: 491-500, 1998.

Zelefsky MJ, Wallner KE, Ling CC, et al.: Comparison of the 5-year outcome and morbidity of three-dimensional conformal radiotherapy versus transperineal permanent Iodine-125 implantation for early-stage prostatic cancer. Journal of Clinical Oncology 17: 517-522, 1999.

Comparison of Treatments for Acute Myeloid Leukemia. The role of bone marrow transplantation (BMT) is unclear in young adults with acute myeloid leukemia (AML); although it can be highly effective, it is an extremely dangerous treatment. In this comparison of BMT and standard chemotherapy, researchers found that patients who received chemotherapy after remission remained free of disease as long as those treated with BMT, and fewer died as a result of the treatment.

Cassileth PA, Harrington DP, Appelbaum FR, et al.: Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. New England Journal of Medicine 339: 1649-1656, 1998.

Adequacy of Psychopharmacological Treatment of Depression Found Wanting. Although modern antidepressant medications are highly effective when administered properly, long-term study indicates that most people with episodes of major depression receive inadequate antidepressant dosages and receive the medication for an inadequate period to permit depressive symptoms to remit. A substantial percentage of these seriously ill people, including those at risk for suicide, moreover, receive no medication. This finding by NIH investigators should serve to spur efforts to provide adequate treatment of depression in the community. [secondary B prevention]

Dawson R, Lavori PW, Coryell WH, Endicott J, Keller M: Course of treatment received by depressed patients. Journal of Psychiatric Research 33: 233-242, 1999.

Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, and Maser JD: Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. American Journal of Psychiatry 156, 1000-1006, 1999.

Oquendo MA, Malone KM, Ellis SP, Sackheim HA, and Mann JJ. Inadequacy of antidepressant treatment for patients with major depression who are at risk for suicidal behavior. American Journal of Psychiatry 156, 190-194, 1999.

Older and Minority Nursing Home Residents with Cancer Experience Inadequate Pain Control Procedures. Cancer prevalence increases with age, and many cancer victims reside in nursing homes. Widely accepted World Health Organization (WHO) protocols for pain management with pharmacological agents have been demonstrated to relieve pain in over 90% of the cancer cases. However, analyses from a five-state Health Care Financing Administration Demonstration Project of almost 1500 American nursing homes revealed that residents are inadequately managed. Over a quarter of patients in daily pain received no analgesic agent. The

oldest patients (those 85 and older) experiencing daily pain were less likely than younger patients to receive pain medication, as were minority residents and those with low cognitive capacity. Solutions to this problem need to account for barriers to pain management such as nursing homes stocking opiates, inadequate staff to monitor opiate administration, and the failure of many physicians to aggressively use analgesic agents in this population.

Bernabei R, Gambassi G, Lapane K, Landi F, Gatsonis C, Dunlop R, Lipsitz L, Steel K, and Mor V: Management of pain in elderly patients with cancer. Journal of the American Medical Association 279: 1877-82, 1998.

Behavioral Training is More Effective than Drug Therapy for Urge Urinary Incontinence. While behavioral training and drug therapy have both been previously demonstrated to be effective treatments for urge urinary incontinence (UI) in older adults, drug therapy is commonly used as the first course of treatment because it is readily available. A recent clinical trial directly compared behavioral training (instrument-assisted pelvic muscle exercises to improve bladder control) to drug treatment for urge UI in older women and demonstrated that behavioral training was significantly more effective than drug therapy in reducing the episodes of accidental urine loss. Thus, behavioral training should be considered the first treatment option given the potential side effects of drug therapy, and to avoid further problems with drug interactions, since older adults are often prescribed multiple medications.

Burgio KL, Locher JL, Goode PS, Hardin JM, McDowell BJ, Dombrowski M, and Candib D: Behavioral vs drug treatment for urge urinary incontinence in older women. Journal of the American Medical Association 280: 1995-2000, 1998.

Exendin-4 Improves Insulin Response in Subjects With Type-2 Diabetes. Present treatments for type 2 diabetes are less than adequate. Sulfonylureas, which are compounds that increase the secretion of insulin, do not affect the natural course of beta cell deficiency, which is the cause of the diabetes. In fact, after a short time the beta cell no longer responds to them. GLP-1 is a naturally occurring gut peptide which also increases the secretion of insulin. The beta cells in type 2 diabetes still respond to GLP-1 and it can normalize blood sugars in this disorder. However, GLP-1 is very short-lived and must be given continuously subcutaneously. Intramural scientists have been examining a long-acting analog of GLP-1, called exendin-4, which was shown in a mouse model to be more potent and long-lived than GLP-1. Study of short-term administration of exendin-4 in diabetic and non-diabetic subjects has now been completed and it has proved to be a very potent and long-lived agent. All thirteen diabetic subjects in the trial responded to exendin-4 by increasing their insulin response on average 10-fold above that induced by glucose alone. A 4-week once-a-day subcutaneous exendin-4 regimen in type 2 diabetic subjects is now underway.

Greig N, Halloway H, Wang Y, Jani D, De Ore K and Egan JM: Once daily injections of exendin-4 to diabetic mice achieves long-term beneficial effects on blood glucose levels. Diabetologia 42:45-50, 1998.

Egan JM, Elahi D: Exendin-4 is insulinotropic in humans, both non-diabetic and diabetic. (Abs. 148) European Association for the Study of Diabetes 1999.

Maintenance of Systolic Blood Pressure Within an Intermediate Range May Reduce Memory Loss Among Elderly Hypertensives. Maintenance of systolic blood pressure (SBP) among treated hypertensive patients may be related to risk of memory decline. Results showed that patients with chronically elevated SBP (> 150 mm Hg) and chronically suppressed SBP (< 135 mm Hg) are associated with greater memory declines on a test of delayed memory recall compared to patients with SBP maintained within an intermediate range. Optimal regulation of SBP within an intermediate range may be a potential modifiable risk factor to prevent or minimize memory loss in older hypertensive patients.

Sacktor N, Gray S, Kawas C, Herbst J, Costa P, and Fleg J: Systolic blood pressure within an intermediate range may reduce memory loss in an elderly hypertensive cohort. Journal of Geriatric Psychiatry and Neurology 12: 1-6, 1999.

Defects in Tumor-Protection Protein May Lead to Cancer. Each cell of the body contains a protein known as p53. This protein, also called the "tumor-suppressor-protein@ is responsible for orchestrating protective responses to stresses, such as exposure to radiation, lack of oxygen and other nutrients. If this protein cannot function correctly for any reason, different kinds of cancer can develop, due to uncontrolled cell division and other cellular reactions. An international team of scientists has determined additional effects of several of these defects on the cell's normal responses to stress, including an increase in chromosome defects such as breaks and duplications. This information is important for development of new cancer therapies and improved selection of therapies for individual patients.

Agapova, L.S., Ivanov, A.V., Sablina, A.A., Kopnin, P.B., Chumakov, P.M., and Kopnin B.P. p53-dependent effects of RAS oncogene on chromosome stability and cell cycle checkpoints. Oncogene 18: 3135-3142, 1999.

Development of Alternative Anti-Inflammatory Drugs through Studies of a Coral Enzyme. Prostaglandins function as key hormones in cancer and in human inflammatory diseases, including asthma. Anti-inflammatory drugs such as aspirin and various steroids work in part by interfering with prostaglandin synthesis. Various undesirable side-effects, however, have led to a search for alternatives. Important in this search is knowledge of how the body makes prostaglandins, a problem that has perplexed scientists for generations. To provide insight into how they may be made in humans, an international team of scientists is studying how they are made in sea corals, the richest known source of prostaglandins. New data suggests avenues for development of new anti-inflammatory compounds that are more effective and have fewer side effects.

Varvas, K., Jarving, I., Koljak, R., Valmsen, K., Brash, A.R. and Samel, N., Evidence of a cyclooxygenase-related prostaglandin synthesis in coral. The allene oxide pathway is not involved in prostaglandin biosynthesis. Journal of Biological Chemistry 274: 9923-9929, 1999.

Regeneration of Bone and Marrow by Transplantation of Bone Marrow Stromal Cells. Although it has been known since the 1960s that bone marrow stroma contains cells with the

ability to form bone, cartilage, hematopoiesis-supportive stroma, associated fat cells, and perhaps other connective tissues, only recently has their utilization for bone regeneration been fully realized. Defects were created in mouse skulls of sufficient size that they would not spontaneously heal. When these defects were filled with a composite of *ex vivo* expanded bone marrow stromal cells and a collagen-based carrier, bone and marrow were completely regenerated. These studies have served as the basis for development of procedures for use in humans with similar, non-healing bone defects, and it is hoped that clinical trials will begin in the near future.

Krebsbach PA, Kuznetsov SA, Bianco P, and Gehron Robey P: Bone marrow stromal cells: Characterization and clinical application. Crit Rev Oral Biol Med 10: 165-81, 1999.

Krebsbach P, Mankani M, Kuznetsov S, Satomura K, and Gehron Robey P: Repair of craniotomy defects using bone marrow stromal cells. Transplantation 66: 1272-78, 1998.

Gene Therapy for Pain. NIH investigators used an adenovirus vector, similar to a common cold virus, to deliver the beta-endorphin gene to the rat spinal cord. The virus particles were injected into the spinal fluid, where they were readily taken up by the protective sheath of connective tissue, called the pia mater, which surrounds the cord. Within 24 hours the sheath cells began secreting beta-endorphin, one of the body's natural sedatives for alleviating pain. The investigators are optimistic that improvements in vector design will result in a single injection that provides long-term gene expression, not only of beta-endorphin, but genes to treat a variety of spinal cord and brain disorders.

Finegold AA, Mannes AJ, and Iadarola MJ: A paracrine paradigm for *in vivo* gene therapy in the central nervous system: Treatment of chronic pain. Human Gene Therapy 10: 1251-57, 1999.

STORIES OF DISCOVERY

Osteogenesis ImperfectaBBrittle Bone Disease

Imagine breaking your ribs when you sneeze. Or fracturing the bones in your spine when the bus you=re riding hits a bump in the road. ABrittle bone disease@ is a genetic defect of collagen, the connective tissue scaffolding upon which bones are built. Technically known as osteogenesis imperfecta, or OI, this mysterious hereditary disorder ranges from mild to severe, depending on the nature of the genetic mutation involved. Mild cases may go undiscovered, but those with the most severe form break so many bones during birth that they do not survive. Some suffer only occasional fractures, breaking about 10 bones in a lifetime; others, with more severe cases may break several hundred.

From 20,000 to 50,000 people may have the disorder, according to the Osteogenesis Imperfecta Foundation. Currently, there is no cure for OI and treatment is usually directed toward preventing bone fractures and caring for fractures that have occurred. Often, people with OI must remain confined to a wheelchair or wear protective braces. Others may undergo a surgical procedure known as Arodding@Bhaving metal rods inserted through the length of the bones to strengthen them and prevent them from breaking.

Diagnosis, too, sometimes proves difficult. OI testing is usually performed by analyzing a skin sample for defective collagen. Although this test can identify most people with OI, about 15 percent of those with obvious signs of the disorder do not have a collagen abnormality that can be detected with the test.

Dr. Joan Marini and her colleagues at NIH have studied the disorder since the 1980s and have unlocked many of its secrets. The NIH researchers began their efforts by pinpointing the numerous mutations that can occur in the gene for Type I collagen, learning that mutations in some parts of the gene cause more severe forms of the disease than do mutations in other parts. This work has resulted in the development of the current methods for diagnosing the condition. Similarly, this research effort provides valuable information on the basic biology of bones, which may be useful in the study of other bone disorders.

For the most part, OI results from only one copy of the abnormal Type I collagen gene. In the past, researchers working with other genetic disorders have tried, with little success, to correct mutations by inserting normal copies of a gene into cells, but this strategy is not suitable for OI.

In contrast, the NIH researchers sought to *prevent* the abnormal collagen from being made. If the defective collagen could be eliminated, they reasoned, OI patients having one normally functioning copy of the gene would experience only a mild form of the disease.

The NIH research team looked to a comparatively new gene technology, which also holds promise for treatment of cancer and AIDS. A plant virusBtobacco mosaic virusBproduces a form of the genetic material RNA that can bind to other types of RNA and prevent them from functioning. Briefly, RNA, or ribonucleic acid, is an intermediary molecule. DNA

(deoxyribonucleic acid), the basic material of genes, gives rise to RNA. In turn, RNA serves as a kind of template upon which proteins are put together.

The tobacco mosaic virus RNA binds to other types of RNA and cuts them into piecesBpreventing the proteins they code for from ever being made. Moreover, this particular type of RNA, which scientists have dubbed the Ahammerhead ribozyme,@ can be tailor made to bind to particular kinds of RNA. Taking advantage of that fact, Dr. Marini and her group have engineered ribozymes that break apart the RNA that codes for the defective Type I collagen RNA. The group inserted the ribozymes into laboratory cultures of skin cells from patients with OI and succeeded in stopping the skin cells from producing the abnormal collagen.

Building on this achievement, the group is now exploring ways to introduce the ribozymes into the bone marrow Astem cells@ which manufacture bone. In theory, the stem cells could be removed from a patient and the DNA that codes for the ribozyme could be added to the cells. After reproducing in laboratory cultures, the cells could then be injected back into OI patients.

The NIH researchers also have used genetic engineering to produce a strain of mice having a defective Type I collagen gene. The researchers are now attempting to insert the ribozyme into the cells of these mice in hopes of providing a treatment for their disorder.

The Cycle of Life

Everything begins with a fateful rendezvous between egg and sperm. After these two cells unite, then divide in two, each progeny cell gets a set of marching orders. Each is told to divide in two again, passing on to each daughter cell a precise copy of the parent cell's genetic material. Throughout the lifespan of an organism, this cycle is repeated billions of times. Amazingly, every cell on the planet has an unbroken lineage that goes back three and a half billion years.

In addition to providing instructions on how and when to divide, these same orders must also tell the cell to "do nothing" in times of dangerBin the presence of damaged DNA, for instanceBso that potential catastrophes like birth defects or cancer are averted. For many decades, basic researchers have been trying to decipher those cellular orders, and at last, their work is turning up answers.

The past 10 years alone have witnessed a remarkable explosion of knowledge in how cells make these important decisions with clockwork precision. As a result, on the horizon may be a new generation of drugs to target cancer cells dividing out of control and an understanding of how some birth defects arise. Fundamental advances in cell cycle research are also yielding powerful molecular diagnostic tools that some clinical researchers are using to tailor cancer therapy.

Decades of Discovery

It was in the middle of this century that scientists first recognized that cells divide according to a prescribed agenda, progressing through recognizable "phases" called G1, S, G2, and finally, M, the period in which a cell actually splits.

Since these early studies, basic researchers have delved deeper into the study of cell cycle transitions and the elements that control them. Their studies of the genetics and biochemistry of the cell cycle have unveiled protective mechanisms that guarantee success the vast majority of the timeBan outcome that might be expected for a process so crucial to life.

One key breakthrough came in 1971, when biochemists first discovered in undeveloped frog eggs a blend of ingredientsBan "activity"Bthat coaxed the cells to mature and then divide. For many years, the identity of this activity, dubbed MPF for maturation promotion factor, eluded researchers. Years later, scientists noted that levels of MPF activity waxed and waned regularly throughout the cell cycle. This finding set the stage for another group of scientists (nearly two decades later, in the late 1980s) to isolate the molecule in pure form, based in part upon its predictable behavior during the cell cycle.

As it turned out, MPF was found to be a central player in the cell cycles of not only frog eggs, but also of all cell types in organisms ranging from single-celled fungi to humans. Purifying MPF allowed scientists to discern that it is composed of two different proteinsBhalf of MPF is a protein called a cyclin and the other half is an enzyme called a kinase (CDK, for cyclin-dependent kinase).

In the 1980s and early 1990s, genetic approaches begun in the early 1970s took center stage and provided a flood of new information on the cell cycle. Working in model organisms like yeast, genetics researchers rapidly turned up components of MPF in many different species, from yeast to humans. At this point, scientists were well-equipped to compare and contrast cell cycle function in different organisms, searching for common themes. In biology, processes that prevail throughout the vast biological kingdom are almost always the most important ones.

The story was the same everywhere researchers lookedBcell cycle function hinged upon the coordinated behavior of CDKs and cyclins. Akin to a motor, CDKs propel the one-way cycle forward, but they only do so when "turned on" by their partner cyclins, whose levels go up and down at distinct, predictable times during the cell cycle. Scientists discovered that two important cogs connecting these gears of the cycle are molecular "housekeeping" activities called phosphorylation and proteolysis. Recently, scientists determined that the latter, a cellular garbage disposal process, helps regulate levels of cyclins, chewing them up when they are no longer needed to activate CDKs and thus allowing the cycle to proceed to the next phase. The other process, phosphorylation, in which proteins are marked with a chemical tag called a phosphate, also plays an integral role. The process of applying and removing phosphates turns on or off both cyclins and CDKs, as well as many other molecules that regulate them.

Keeping Everything in Check

In the late 1980s, scientists found that nestled between each of the cell cycle phases are sophisticated systems of checks and balances. These protective processes, called "checkpoints," are ordered collections of genes and proteins that can step into play in a snap if something goes awry. Naturally, with such a complicated and important task as cell division, these checkpoints keep quite busy. Incomplete copies of genes or a variety of other "danger" signals grind the cycle to a screeching halt. Once the appropriate molecular deeds have been done, or the damage has been repaired, the molecular brakes are taken off the checkpoints, and the cycle proceeds.

So important are the checkpoints, scientists believe, that without them cancer would happen all the time. In fact, in the mid-1990s, scientists discovered that a gene encoding a "tumor suppressor" protein named p53 performs its protective role by switching on yet another tumor suppressor, called p21. Many cancers occur when "misspellings" in the p53 gene produce a defective p53 protein that cannot perform its tumor-suppressing function.

Bearing Fruit

The years of basic research devoted to identifying how the cell cycle works have now begun to pay off clinically. Researchers enthusiastically portend that the cell cycle field is poised to deliver health benefits to cancer patients in the near term, perhaps within the next decade. Currently in the clinical trials pipeline are scores of potential drugs targeted to either beef up or tone down levels of cell cycle molecules. In the meantime, some clinical researchers are using basic cell cycle research knowledge to predict cancer outcomes and tailor chemotherapy. Recent studies have shown that levels of two human cell cycle proteins, cyclin E and the CDK inhibitor (and tumor suppressor) p27, fluctuate predictably with breast and prostate cancer progression.

Such prognostic information can be extremely valuable to doctors treating patients, enabling them to decide on how aggressively to treat a tumor.

Artificial Skin Offers Hope for Burn Victims

A 3-year-old girl grabs a frying pan of boiling-hot oil off the stove . . . while playing with matches, a 5-year-old boy ignites his pajamas . . . the tip of an 80-year-old woman's housecoat catches on fire as she reaches for a teakettle on the stove . . . .

Each year in the United States, more than 2 million burn injuries resulting from situations such as these demand medical attention. As many as 10,000 people die every year of burn-related infections, and tragically, many of the victims are children. The good news is that, in recent years, survival statistics for serious burns have improved dramatically. Twenty years ago, second- and third-degree burns covering half the body were routinely fatal. Today, patients with severe burns encompassing 90 percent of their body surface typically survive.

Driving burn injury survival statistics upward have been fundamental advances in basic research aimed at understanding how skin and the rest of the body respond to damage caused by burns.

Skin Loss Can Deal Lethal Blow

More than simply a protective covering, skin is a highly dynamic network of cells, nerves, and blood vessels that serves the body in diverse ways. Skin plays an important role in preserving fluid balance and in regulating body temperature and sensation. Immune cells resident in skin help the body prevent and fight disease. Burn-induced skin loss affords bacteria and other microorganisms easy access to the warm, moist, nutrient-rich fluids that course through the body, while at the same time it provides a conduit for the rapid and dangerous loss of these fluids. Extensive fluid loss can thrust a burn or trauma victim into shock, a life-threatening condition in which blood pressure plunges so low that vital organsBsuch as the brain, heart, and kidneysBsimply cannot get enough blood (and thereby oxygen) to function.

Replenishing skin lost to severe burns is an urgent matter in the care of a burn patient. In the case of burns covering a significant portion of the body, two immediate tasks come to the fore. First, the burned skin must be stripped, then the unprotected underlying tissue must be quickly covered. Antibiotic treatment buys some time by limiting potentially deadly infections. Despite being seemingly obvious, these important steps in the immediate care of a burn patient are the result of decades of carefully conducted research on how the body responds to burn injury.

In the early 1970s, a group of burn injury researchers reviewing the grim mortality statistics facing burn patients at the time reasoned that the complete removal of badly burned skin (as opposed to letting it slough off over time) might offer greater protection against wound infection and improve the very poor prognosis that these patients faced. Recognizing that a necessary follow-up would be immediate and permanent skin replacement, these scientists pioneered the use of skin from related donors (such as family members with similar genetic markers). But doing so required that the burn patient be given powerful immunosuppressant drugs to dampen the immune system and prevent rejection of the graft. Unfortunately, crippling the patient's immune system in this way posed many serious problems. The need for some form of "artificial skin" became urgently apparent.

Soon thereafter, with support from the National Institutes of Health, the researchers developed the first version of an artificial skin system called Integra J. Every similar artificial skin product that has since been researched and developed hinges upon the conceptual framework that eventually yielded this product. Today, Integra J is used to treat 1 of every 10 severely burned patients in the United States and is the top-selling skin substitute in the world.

Artificial Skin: Born of a Marriage Between Engineering and Medicine

The brainchild of a trauma surgeon and a mechanical engineer, Integra J is a prime example of the extraordinary value of collaborative research.

Integra J contains no living components and is not actually designed to be a replacement skin. Rather, it supplies a protective covering and a pliable scaffold onto which the patient's own skin cells can "regenerate" the lower, dermal layer of skin destroyed by a severe burn. Integra J consists of two layers, just as living skin is structured. The bottom, dermal-like layer is composed of a matrix of interwoven bovine collagen (a fibrous cow protein) and a sticky carbohydrate (sugar) molecule called glycosaminoglycan that mimics the fibrous pattern of dermis. This matrix is then affixed to a removable upper layer: a medical-grade, flexible silicon sheet that mimics the epidermal, or surface, layer of skin. The product looks somewhat like translucent plastic wrap.

After first removing tissue destroyed by the burn, a burn surgeon drapes Integra J over the wounded area of the patient and leaves it there for 2 to 4 weeks, during which time the patient's own cells make their way into the matrix and create a new dermis. The top layer of Integra J is then removed, and a very thin sheet of the patient's own epithelial cells is applied. Over time, a normal epidermis (except for the absence of hair follicles) is reconstructed from these cells.

On the Horizon

Integra J moved from the research lab to licensing, testing, and production by Marion Laboratories of Kansas City, Missouri. The product is now being manufactured and sold by Integra LifeSciences Corporation of Plainsboro, New Jersey. After extensive clinical testing, Integra J received FDA approval in the mid-1990s, and is now enjoying wide use for the treatment of severe burns and other serious skin injuries. Through an NIH Small Business Innovation Research grant, Integra LifeSciences is currently investigating what potential benefits adding a molecule that coaxes new growth of blood vessels within the original matrix might add to the quality and/or speed of skin regeneration of a burn-wounded area. Early results are promising, showing that this approach can speed healing and improve the physical appearance of the once-burned area.

Other scientists have succeeded in expanding a small number of real skin cells into a transplantable sheet that can be layered on top of Integra J that has been bathed in a nutritious mix of growth factors. The method has been evaluated in a small number of patients, and so far appears to offer a significant advantage over other currently available technologies.

Turning Blue Babies Pink

In 1944, Eileen Saxon, a blue, frail 15-month-old child weighing little more than a newborn, was anesthetized with drops of ether and woke up a pink pioneer in congenital heart disease. She had the first Ablue baby@ operation conceived and perfected by the team of Alfred Blalock, Helen Taussig, and Vivien Thomas at Johns Hopkins, which revolutionized congenital heart disease treatment. Her postoperative course was rocky. The sophisticated monitoring commonplace in pediatric hospitals today was nowhere in evidence. Instead, the surgical team visited frequently, and a pediatrician set up a stretcher next to Eileen=s bed, remaining by the child=s side continuously for the first 48 hours.

Eileen=s malformation, tetralogy of Fallot, is the most common cause of cyanotic (blue) congenital heart disease. Pathologists began describing the constellation of features from autopsy specimens in the late 1600s, and Fallot, writing in 1888, summarized the four consistent features: a large hole between the 2 pumping chambers of the heart, an underdeveloped blood supply to the lungs, an abnormally positioned aorta, and thickening of the right ventricle. For over 250 years, physicians could only stand by and watch while children with cyanotic heart conditions suffered through childhood, rarely surviving into adolescence. The Blalock-Taussig shunt became the medical equivalent of a shot heard =round the world.

Amazingly, Eileen was taken to the operating room for heart surgery without any direct imaging of her heart to pinpoint the diagnosis. In 1944, doctors had at their disposal only primitive electrocardiography, chest X-rays, and fluoroscopy to augment patient history and physical examination in making a cardiac diagnosis. From these tools, inferences could be made about the shape of the heart and the size of the ventricles, but direct confirmation came only at autopsy. The success of the blue baby operation in providing the first therapy for congenital heart disease led to an explosion of interest in better diagnostic tools. Fortuitously, this coincided with the establishment of the National Heart Institute within the NIH (now the National Heart, Lung, and Blood InstituteBNHLBI) in 1948. From its beginning, the Institute supported research in the new field of pediatric cardiology. In 1950, it awarded Dr. Blalock $12,000 to study surgical approaches to congenital heart disease. His work built on a previous award to Johns Hopkins to study radiographic and angiocardiographic diagnosis of congenital heart disease. Researchers at Hopkins assembled a primitive angiographic apparatus that would advance film cassettes using a rope pulley for serial imaging during the dye injection. More often than not, one of them would have to remain under the contraption, guiding the cassettes so they did not fall on the floor, and simultaneously trying to avoid X-ray beams. From this humble beginning arose modern angiocardiography, which meant that, for the first time, anatomy inside the heart could be visualized in the living child outside the operating room.

Whereas the Baltimore team sought to create a shunt to the pulmonary artery, Dr. Robert Gross was the first surgeon to eliminate a naturally occurring shunt, the ductus arteriosus. This vessel allows blood to bypass the lungs in the fetus, and is programmed to close shortly after birth. Occasionally, however, it does not close, and can overload the left side of the heart, leading to heart failure. In 1938, Dr. Gross was a surgical resident at the Children=s Hospital in Boston. He approached the Chief of Surgery with a proposal to tie off the ductus in a child in whom the

diagnosis had been made by auscultation (listening with a stethoscope). The Chief rejected Gross= proposal in no uncertain terms, but persistence paid off. While the Chief was on vacation, Gross successfully ligated the ductus in a 7-year-old child who survived and did well.

The next major breakthrough was the development of heart-lung bypass, which allowed surgery to be performed on the inside of the heart in a bloodless field. Dr. John Gibbon, a surgeon at the Massachusetts General Hospital, began work on a heart-lung bypass machine in the 1930s. His work was interrupted by World War II, but he resumed it after the war with support from the NIH and collaboration with IBM engineers. His first patient was a 15-month-old baby who died, in part, because her preoperative diagnosis was incorrect. Success came with his second patient, an 18-year-old girl with a hole between the two top chambers of her heart (atrial septal defect), who survived the first heart-lung bypass procedure in 1953. Although many refinements were needed to bring bypass into widespread use, it was a big improvement over previous practices of packing the patient in ice and doing Abeat-the-clock@ surgery, or of so-called cross-circulation, in which the blood supply of a parent and the child were connected, and the parent=s heart provided the circulating pump for the child. This latter procedure has been described as the only surgical procedure with the potential for 200 percent mortality, and it was quickly replaced.

Through courage and resourcefulness on the part of patients and physicians, it had now been demonstrated that both open- and closed-heart surgery were feasible on infants and children. Angiography provided general diagnosis of congenital heart disease, but it was invasive, requiring catheters to be placed through peripheral blood vessels into the heart. With successful surgery becoming more widespread, there was increased interest in developing noninvasive imaging. In 1957, the NIH awarded a grant to Alexander Nadas at Boston Children=s Hospital to study phonocardiography in congenital heart disease. A microphone was placed on the child=s chest so that the sounds made by murmurs and by heart valves opening and closing could be recorded on paper for further study. From these tracings, physicians quantitated the degree of narrowing of heart valves and recognized additional heart sounds that indicated heart disease.

The use of ultrasound waves to visualize the heart (echocardiography) was an astute clinical application of sonar technology developed during World War II. Fuzzy images barely recognizable as the heart were produced for the first time in 1954. The scientific details of echocardiography were worked out largely by physicists and engineers, including Dr. Olaf Von Ramm, a biomedical engineer at Duke University. Dr Harvey Feigenbaum, a cardiologist at the Indiana University School of Medicine was the first to realize the practical potential and to bring echocardiography into clinical practice. Both researchers, as well as many other adult and pediatric cardiologists working on echocardiography, were supported by the NIH and continue to receive NIH funding. Echocardiography was first used in children in the early 1970s. By the 1980s, ultrasound techniques had been refined, color imaging had been added, and image resolution had improved to the point that noninvasive diagnosis of congenital heart defects could be reliably performed in utero. Dr. von Ramm now is applying his energies and NIH funds to develop 3-D echocardiographic imaging, first introduced in 1995. Commercial 3-D systems, now in experimental use in both adults and children, allow researchers to peer inside of hearts in ways that are not possible with conventional 2-D imaging.

Once hearts could be imaged, and congenital heart disease could be diagnosed accurately, epidemiologic studies could be done to determine the patterns of congenital heart defects in populations. The landmark Baltimore-Washington Infant Study, funded by the NIH in the 1980s, is the gold standard for categorizing types of congenital heart disease, estimating their occurrence among live-born infants, and analyzing possible risk factors. From this study we learned that about 1 percent of newborns (about 40,000 per year in the United States) have some form of congenital heart disease, making this the most common birth defect.

A child born 50 years ago with a heart defect had a dismal prognosis. Today, that same child will likely live a long and productive life. Looking back over the past half century, one cannot help but be awestruck by the incomparable progress in pediatric cardiology. In no other pediatric specialty has the medical landscape changed so dramatically, from near-certain mortality at an early age, to prenatal diagnosis and, in some cases, prenatal therapy. Delicate repair of complex congenital heart defects can now be undertaken in the newborn period, on infants weighing as little as 3 pounds. These accomplishments are founded on the courage of families willing to submit their desperately ill children to unproven procedures to forestall death, and to the intellect, persistence, and skill of physicians and researchers who pioneered innovative therapies. The NIH has been a constant partner in the research that supported every step of this miraculous journey, from the development of echocardiography, angiocardiography, and surgical procedures in children to the now common clinical use of genetic testing for abnormalities associated with congenital heart disease. Looking forward to the next 50 years, the NIH has taken the leadership role in supporting research into the molecular underpinnings of normal and abnormal heart development. With new molecular and physiologic tools, understanding the reasons why heart development goes awry may lead to therapies unimagined today.

Multiple Applications of Gene Transfer to Salivary Glands

A successful 43 year old executive, preoccupied with a major corporate acquisition proposal, ignores a bump on her tongue she first noticed while brushing her teeth. A few weeks later, after her business efforts have proven successful, she again notices the now slightly larger bump and decides to see her dentist. The dentist biopsies a small white spot on the tongue surface. A few days later the report comes back: squamous cell carcinoma. The dentist informs the patient, and refers her to an oral surgeon who recommends extensive intra-oral surgery, including a partial tongue resection, accompanied by radiation therapy. The prognosis is good and the patient commences therapy. The surgery is successful and the radiation treatments are completed. One year later the patient returns to her surgeon for a follow-up visit and gets an excellent report: no evidence of tumor recurrence. The surgeon notices the patient is pleased but not ecstatic, and asks if anything is wrong. She answers that while she is very happy there is no evidence of tumor, and the tongue resection has healed well, she has had problems ever since the radiation therapy. Her mouth is dry and sticky, and she has trouble swallowing many foods during meals. She complains of frequent episodes of thrush, and problems speaking rapidly and fluently during business negotiations. She asks what can be done. The surgeon answers, AUnfortunately nothing, because radiation damages the cells that make saliva. But remember, you are tumor free.@

Each year about 40,000 people in the US, and about 500,000 worldwide, suffer from some form of cancer in the head and neck region. In the US and other industrialized countries most such patients experience radiation therapy as part of their treatment. Cancer removal is the top priority, but the most significant post-treatment complication for such patients is lack of saliva. Most people pay little attention to this oral fluid until it is gone. Saliva plays a crucial role in everyday healthBdefending against bacterial, viral and fungal pathogens, helping to prevent tooth decay, and facilitating normal feeding and speaking behaviors. Scientists have recognized that radiation damages salivary glands since the time of the pioneering research of Marie and Pierre Curie. Despite longstanding knowledge of this association, there is still no conventional therapy that can either prevent or repair such damage.

Nearly 10 years ago, this lack of an adequate treatment led NIH scientists to hypothesize that perhaps the tools being developed in the fledgling field of gene therapy could be brought to bear on salivary gland dysfunction. At the time, the notion that gene transfer might be used to address a significant quality-of-life problem, such as the lack of saliva experienced by irradiated patients, was highly unusual. Most people interested in gene therapy envisioned its use only for correction of in-born errors of metabolism and other genetic defects, or perhaps for use with certain acquired life-threatening diseases. Over time, NIH has consistently supported basic research on saliva and salivary gland secretion. Building on this fundamental understanding of how salivary cells function, the scientists devised a scheme to correct gland damage using gene transfer.

Salivary glands have two general types of cells; secretory and absorptive. The secretory cells are damaged by irradiation while the absorptive cells generally survive. Importantly, there is easy clinical access to salivary gland cells directly through the gland openings into the mouth. This

circumstance would allow them to have direct contact with all cells remaining in the tissue, i.e. every cell in a salivary gland is technically in direct contact with the mouth.

In a series of studies, the investigators showed that both secretory and absorptive salivary cells were excellent targets for *in vivo* gene transfer in several animal models. By 1997, a successful proof of concept study in a rat model demonstrated that it was possible to dramatically increase saliva flow from radiation-damaged glands by using the transfer of a single gene that encoded a water channel. While irradiated glands exposed to a control gene transfer vector secreted saliva at ~35% of that seen in normal rats, animals treated with the water channel gene produced saliva at levels indistinguishable from control non-irradiated animals. Additional studies are required before this approach is ready for application in patients. However, the animal studies suggest that in the future it may be possible to help patients with impaired saliva flow due to irradiation.

The research on radiation-damaged salivary glands also stimulated both intramural and extramural scientists to explore additional possible applications of gene transfer to salivary glands. One application was gene transfer to normal glands to augment the spectrum of proteins already being secreted into saliva. This could be used to treat specific disorders in the upper gastrointestinal tract. An example of this was genetically engineering rat salivary glands to secrete a potent antifungal protein able to kill fungal species resistant to conventional antifungal drugs. Antifungal drug resistant candidiasis, on the mucosal tissues of the mouth, pharynx and esophagus, is often seen in immunosuppressed individuals, such as patients receiving chemotherapy or organ transplants and persons with AIDS.

A third and highly novel application of salivary gland gene transfer was pursued in parallel work by intramural and extramural scientists. This application used normally functioning glands as natural slow release devices to supply a needed protein for a systemic single protein deficiency disorder, e.g. diabetes or growth hormone deficiency. Some endocrine secretion into the blood stream by salivary glands, and the ability of the glands to produce and secrete large amounts of protein**,** had been known for some time. In independent animal studies, using different gene transfer methods, the two groups demonstrated that salivary glands could be genetically engineered to produce hormones which were secreted into the bloodstream and worked effectively elsewhere in the body. The approach was so successful that a biotechnology firm was established with the sole purpose of utilizing salivary gland gene transfer for the secretion of various endocrine factors to treat systemic diseases.

What started as a search for a treatment to restore radiation-damaged salivary glands to normal function has led to multiple explorations of the application of gene transfer to salivary glands. This expanding array of applications offers promise for future treatments addressing clinical problems that include diseased salivary glands, opportunistic infections, and systemic disorders.

Using Tamoxifen to Prevent and Treat Cancer

The journey of scientific discovery is neverending, and demands both perseverance and collaboration among researchers and clinicians in order to reach its milestones along the way. This was true in the more than 30- year process of discovery and development of tamoxifen. First developed as a breast cancer treatment, tamoxifen now has been proven to help decrease the risk of breast cancer in women at high risk for developing the disease. The discovery of tamoxifen=s dual role was fostered by the dedicated efforts of many researchers around the world who pursued the use of tamoxifen as a treatment and ultimately recognized its potential for breast cancer prevention, and by the efforts of thousands of patients who volunteered for clinical trials testing tamoxifen.

Tamoxifen, first discovered in 1962, is an anti-estrogenBa substance that stops estrogen from working in specific tissues by preventing the hormone from docking in estrogen receptors found in these tissues. Because of this activity, tamoxifen was first tested as a contraceptive; however, women in the clinical trials who took tamoxifen remained fertile.

Realizing that tamoxifen was not an effective contraceptive, scientists looked for other ways the compound could be used. Through these investigations, they discovered that tamoxifen=s anti-estrogen activity appeared to be selective: it only stopped estrogen from working in certain tissues, such as breast tissue. Knowing that estrogen must bind to its receptors in breast cancer cells to promote tumor growth, and that tamoxifen prevents estrogen from reaching its receptors, scientists began to wonder if the drug might stop breast cancer growth. Therefore, researchers began looking at the drug=s ability to combat the growth of human breast cancer cells in animals, as well as in cancer cells grown in the laboratory. In both settings, tamoxifen successfully robbed the cancer cells of the estrogen they needed for tumor growth. These results led to testing of tamoxifen as a treatment for patients with advanced breast cancers. These first clinical trials were successful, and in 1977, the Food and Drug Administration (FDA) approved tamoxifen for therapy of advanced breast cancer.

Tamoxifen=s success as a treatment for advanced breast cancer fueled many scientists= desire to continue looking for new ways to use the drug to help cancer patients. Tamoxifen was next tested with success as an adjuvant therapy, a treatment given following surgery. Its success as an adjuvant therapy and in treating women with lymph-node involvement led to FDA approval of tamoxifen=s use for these patients in the early 1980s.

As the results of the different trials were reported, the sharing of information among researchers in the laboratory and clinic became critical to refining the design of new trials and uncovering trends in the data. When this growing pool of data was analyzed, three themes began to emerge: women who received tamoxifen had increased rates of survival; women who took the drug had fewer recurrences of cancer; and, it appeared that tamoxifen could decrease the risk of getting another cancer in the opposite breast. In addition, studies in animals showed that tamoxifen could prevent breast cancer.

The results in women with breast cancer suggested that tamoxifen could prevent new breast cancers. But could the drug prevent breast cancer in women who had never been so diagnosed? In 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) launched the NIH-funded Breast Cancer Prevention Trial (BCPT) to find out.

In this landmark trial, over 13,000 women at high risk for developing breast cancer volunteered and were randomly assigned to receive either tamoxifen or a placebo. In 1998, the historic results were announced: the data showed that tamoxifen reduces the rate of developing primary breast cancer by 49 percent in women who are at high risk for developing the disease. Potentially severe side effects, such as an increased risk of developing endometrial cancer in women over age 50, and a risk of developing blood clots in the major veins and lungs (similar to hormone replacement therapy), were noted. After noting the observed benefits and side effects, in October 1998, the FDA approved the use of tamoxifen to reduce the risk of breast cancer in women at high risk.

Tamoxifen=s story has not yet come to a close. Researchers are already creating and testing a second generation of breast cancer prevention agents, such as raloxifene, which may help prevent the disease without some of tamoxifen=s potential side effects. In 1999, the NSABP launched the Study of Tamoxifen and Raloxifene (STAR), a trial that is comparing the two drugs= ability to prevent the onset of breast cancer in high-risk, post-menopausal women, as well as comparing the side effects of the two drugs. Approximately 22,000 women will participate in this important study.

As we continue our search for effective methods of preventing breast cancer in all women, we can mark the discovery and development of tamoxifen as a major milestone in medical history. Because of tamoxifen=s unprecedented success at lowering the risk of getting breast cancer, the development of tamoxifen has established a new avenue of prevention research that should continue to foster prevention discoveries and successes well into the future.

Islet Transplantation for Type 1 Diabetes

Sally, a 9-year old, faces the need for daily, multiple injections of insulin just to survive. She is an insulin-dependent, or type 1, diabetic and her body is unable to produce insulin, a hormone secreted by the islet cells of the pancreas that regulates glucose metabolism. Unlike nondiabetics, who have an automatic system for sensing levels of sugar in the blood and delivering appropriate amounts of insulin, Sally must manage her blood sugar on her own. In her lifetime, she will measure her blood sugar, by pricking her fingers, as many as 70,000 times and take over 50,000 insulin shots. She must follow a strict diet and monitor closely all physical activity. Despite adherence to such a demanding and overwhelming routine, she is likely to suffer from life-threatening complications such as coma. Her diabetes may progress to serious diseases of the eye, kidney, heart and nervous system, shortening her lifespan by up to 15 years. Blood circulation may become so poor that limbs may need to be amputated.

Sally is not alone. Diabetes affects an estimated 16 million people in the United States. Of this number, approximately 800,000 people have type 1 diabetes, an autoimmune disease in which the body=s immune system attacks its own insulin-producing beta cells in the pancreas and destroys them. The pancreas then produces little or no insulin, requiring the individual to receive their insulin from an external source; through daily, oftentimes multiple, injections. Each of these 800,000 individuals bears the enormous burden of managing their disease; working closely to maintain a delicate balance among diet, exercise and insulin.

For people with type 1 diabetes, insulin is a therapy, not a cure, and does not provide protection from the severe long-term complications of the disease. For decades, researchers have been searching for better ways to treat, prevent, and ultimately cure type 1 diabetes. They have been rigorously pursuing means to regulate blood glucose levels in type 1 diabetic patients and to restore insulin-producing capacity through transplantation of the whole pancreas or of islets isolated from donor pancreas. Successful transplantation of the whole pancreas is presently the only means to re-establish normal blood glucose regulation. However, this procedure does entail major surgery. Therefore, scientists have been concentrating on simpler methods, replacing only the islets. However, experimentation thus far has yielded very limited results. Since 1974, more than 300 islet transplants have been performed in the United States. The islets have worked in less than 35 percent of these patients, and fewer than 10 percent have been able to stop taking insulin even for a short period of time.

Success has been hampered by numerous factors. Improved methods for preserving donor pancreas for optimizing islet isolation and survival, as well as improved methods for preparing large quantities of islets for transplantation are needed. Immunosuppressive agents ,used to prevent rejection, can also cause injury to the islets themselves before they can begin producing insulin. These agents also cause such severe side effects that the cure is sometimes worse than the disease. Initially, doctors failed to recognize that the individual=s with type 1 diabetes immune system was once again attacking and destroying the new islets in the same manner it did the old ones. They thought the problem was rejection of the transplanted tissue, a problem that can occur with all organ transplants.

Through research conducted and supported by NIDDK investigators, vital groundwork has now been laid for overcoming many of these challenges, including important discoveries in immunology, cell biology, transplant biology, and autoimmune diseases. For example, researchers have found that rejection of transplanted islets can be avoided if the immune system is Are-educated@ so that it will accept the new islets. To re-educate the system, one function of critical cells active in the immune response, called T-cells, has to be switched off. T-cells require a two-stage activation process to protect the body from foreign substances. One stage recognizes that the foreign substance is not a normal part of the body. The second stage of the system, called Aco-stimulation,@ leads to the production of other T-cells that attack and destroy the foreign substance. By blocking co-stimulation, the immune system learns to accept the foreign body as Aself,@ a process called Atolerization.@ Therapies based on tolerization raise the possibility of modifying immune system reactions instead of having to suppress the entire system with anti-rejection drugs.

Since 1992, research studies conducted and supported by the NIDDK have demonstrated that these immunomodulation agents could prevent rejection of transplanted organs and tissues in rodents. In 1997, researchers found agents which blocked the second stage of the T cell response which prevented the rejection of transplanted kidneys in rhesus monkeys. The monkeys tolerated the medicines well without any apparent toxicity and showed no signs of graft rejection for at least six months after the transplant. Researchers also found that the animal=s immune system did not appear to be impaired by the therapy. Building on initial animal trials, in June of 1999, the same researchers demonstrated that a new agent, taken for only a few months after transplantation of a kidney, led to long-term acceptance of the new organ in primates. To increase the challenge, both donor and recipient monkeys were mismatched for a series of proteins found on the surface of the cells that help the immune system distinguish Aself@ from Aforeign.@ In control animals that did not receive the agent, this mismatch led to rapid rejection of the organs. More than a year later, test animals remain alive and well.

Advances in this technique has not been limited to only kidneys. NIDDK-supported researchers have demonstrated similar results using the same agent in three different species of primates, the closest animal model to man, that have received islet transplants. Transplantation of an adequate number of viable islets resulted in successful engraftment and insulin independence in these studies. Also, there did not appear to be an inhibitory effect of the agent on islet function and there was no evidence of drug-induced toxicity or infectious complications. In three treated animals, the agent was halted after a year and, one year later, these animals still showed no signs of rejection.

It is still a long way from animals to humans, but scientists involved in both studies are testing the agent for safety in small, carefully designed, human trials. In one study, immunomodulation therapy will be given to patients receiving a kidney transplant for end-stage renal disease. Later, researchers plan to transplant islets into individuals with diabetes caused by removal of the pancreas or with clearly documented maturity onset diabetes of the young (MODY). If these initial studies show that immunomodulation methods can prevent organ rejection, the study will be expanded to determine whether individuals with type 1 diabetes can benefit.

The second trial involves transplantation of islets into individuals with type 1 diabetes that have not yet developed the long-term complications associated with the disease. This has been made feasible, in part, by the development of an automated method for isolating large numbers of islets from a single pancreas. This method has made it possible to isolate enough islets from one pancreas to transplant to one patient. Until recently, as many as five or six organs were needed to carry out one transplant. The goal of this study is to determine not only whether the drug will stop or prevent rejection of the transplanted islets, but also whether it will prevent the body from attacking and destroying the new islets.

Despite numerous advances, obstacles to islet transplantation still remain and must be overcome before this technique can be used routinely as a treatment for diabetes. Prominent among these barriers are generating an adequate supply of donor islets and protecting the graft from rejection. Currently, the demand for islets still exceeds the supply of harvested organs. Scientist are now examining new ways to develop alternative sources of islets through genetic engineering, islet expansion and regeneration, and isolation from other species such as pigs. Yet, for the first time in decades, there is hope for patients with diabetes that a cure may be on the horizon.

Psoriasis

As many as 5 million Americans may suffer from psoriasis, a disfiguring skin disease that can cause a lifetime of suffering and in some cases may lead patients to become social recluses. Rough, red scaly lesions thicken the skin, and itching and burning are common. In addition, some people with psoriasis are afflicted with joint inflammation, called psoriatic arthritis.

Throughout the years, research has tracked psoriasis symptoms to a number of sources. Many years ago, scientists considered psoriasis a disease of skin cells, a growth abnormality that made these cells proliferate and form lesions. NIH-supported studies showed that in people with psoriasis, the outer layer of skin, the epidermis, regenerates itself in 2 days rather than the normal 14 days. Accordingly, therapy was developed to poison these rapidly dividing cells, but the treatments (frequently anticancer drugs or high doses of ultraviolet light) were fraught with potentially serious side effects.

The next phase of scientific investigation revealed that immunosuppressive drugs used to prevent graft rejection were effective in patients with psoriasis, although the drugs were not inherently antiproliferative. Subsequent research suggested that immunologically active cells, T cells, may stimulate epidermal cells to proliferate and therefore psoriasis may be a disease of the immune system. Under normal conditions, T cells help protect the body against infection and disease; but scientists now think that in people with psoriasis, T cells may react against the body=s own tissues, triggering inflammation and excessive skin cell reproduction. Thus, therapies have been developed to reverse this T cell response, and current studies involving immune-modifying therapies promise more effective, less toxic agents.

Also being investigated are genetic aspects of psoriasis. Researchers are studying large families affected by psoriasis to identify a gene or genes that may make some people more susceptible to the disease. Molecular biologic and molecular genetic techniques are focusing on the interaction of the immune system with the proliferating skin cells. Insights gained should enable better understanding of the nature of the disease and improved approaches to treatment and prevention. The quest for the basis of psoriasis continues on many fronts.

Complementary and Alternative Medicine (CAM): Ever More Popular, It=s A User Friendly Option

Public interest in alternative medical treatments and their ability to ameliorate pain and disease has steadily increased in recent years. Against this backdrop and concurrent with its development, the Congress created the NIH National Center for Complementary and Alternative Medicine (NCCAM). The mandate is clearly enunciated well known: the conduct and support of basic and applied research and training and information dissemination to practitioners and the public.

CAM use and expenditures have increased significantly since the decade=s onset. Several researchers have concluded that this heightened interest is the result of more people seeking alternative therapiesBrather than established consumers visiting CAM practitioners more often. Various studies show that people appear quite willing to pay out of pocket for CAM services. Accordingly, the question arises: what factors (e.g., personal, social, cultural) motivate one=s decision to use alternative therapies? Scientists have learned that multiple factors are involved.

However, just as the Center=s name implies combining traditional and alternative medicine to augment and improve disease treatment options, analyses of patients attitudes toward CAM reflect the same. Researchers have established that most CAM consumers are not dissatisfied with traditional medicine. Rather, more people are utilizing CAM practices because they consider them compatible with their own values, beliefs, and philosophy toward health and life.

Studies throughout the 1990s indicated that few people, in fact, rely primarily on alternative forms of health care. The vast majority appear to use CAM therapies in conjunction with, or as a complement to, conventional treatment. The percentage of people who seek the services of both a medical doctor and alternative practitioner for a single condition has increased from 1 in 5 to 1 in 3 since the beginning of the decade. Consumer responses indicate that the most influential factor in people=s decision to use alternative health care may be its perceived efficacy. People want relief from symptoms and will use therapies they believe provide it.

CAM techniques are an increasingly popular choice. A 1990 survey estimated that approximately 33 percent of all American adults (about 60 million people) used at least one alternative medical therapy during that year. This proportion increased markedlyBto 42 percent, or 83 million peopleBby 1997. During the same period, the total number of CAM practices used rose some 65 percent, from 577 therapies per 1000 people to 953 per 1000. Largest increases were in the use of herbal medicine, massage, megavitamins, self-help groups, folk remedies, energy healing, and homeopathy. Another statistic likewise reflective of an increasingly CAM-friendly public: approximately 22 million people saw an alternative medical practitioner in 1990; seven years later an estimated 39 million did so.

Then and now, chiropractic, relaxation techniques, and massage therapy were the most commonly used CAM techniques. Interestingly, though, there appear to be only a handful of therapies (e.g., massage, chiropractic, hypnosis, biofeedback and acupuncture) for which a majority of users formally consult a practitioner. Unsupervised use evidently remains the

preferred method for most other alternative therapies. Studies illustrate the particular popularity of CAM among baby boomers: 1 of every 2 people ages 35 to 49 reported having used at least one alternative therapy in 1997. However, there appear be to a large number of Astealth@ CAM users, as the extent to which people disclose their use of alternative therapies to their physicians remains low (estimated disclosure less than 40 percent). These findings demonstrate that physicians need to ask about patients= use; likewise, patients need to be more forthcoming in disclosing their own CAM use.

ResearchBas well as the absence of routine patient-physician discussion of CAMBsuggests that if heath care providers are to help patients make safe and informed treatment choices, they should improve their awareness of alternative practices. In particular, providers of traditional health care must enhance their understanding of the nature and efficacy of CAM therapies and why patients seek them. This Adon=t ask, don=t tell@ tendency reflects the need to develop strategies for professional dialogue. This is particularly important since, according to a recent study, physicians are largely unfamiliar with malpractice implications of referring patients to CAM practitioners and little is known about the malpractice experience of practitioners who deliver CAM therapies. Regrettably, the prospect of improving disease treatment outcomes by combining traditional medicine and CAM must overcome longstanding rivalry between conventional health care and CAM practitioners. Clarification of the medical liability issues should help to promote greater integration of patient care.

A fundamental and all too frequent obstacle is physicians= lack of knowledge about CAM practices and their relative effectiveness. Research has concluded that opening a dialogue between physicians and CAM practitioners is crucial to better health outcomes for those who choose alternative therapies. This need will only increase as public use of CAM increases and health insurers include additional non-traditional therapies among the benefits they offer.

To that end, evidently >seeing CAM is believing= among primary care physicians. A 1998 study found that biofeedback and relaxation, counseling and psychotherapy, behavior medicine, diet, and exercise were the therapies in which physicians were most often trained, regarded as legitimate, and have or would use in practice. Conversely, less than 30 percent indicated that acupuncture, herbal medicine, and homeopathic medicine were legitimate medical practice. Traditional Oriental medicine, Native American medicine and electromagnetic treatments were even less familiar and least accepted by physicians. Those with 22 or more years in medical practice had the least favorable attitudes toward CAM. These findings illustrate that familiarity plays a role in CAM=s acceptance by mainstream medicine. It is encouraging to note that increased public interest in CAM appears to be influencing changes in medical school course offerings [e.g., in 1995, researchers identified 33 medical schools and 75 family practice residencies with formal instruction in alternative medicine (with more in the offing)].

Congressional, physician, patient, and scientific interest in CAM are all increasing. These collective interests, however, are essentially uncoordinated. Accordingly, NCCAM is uniquely positioned to identify and support rigorous scientific research and to provide information to the public and providers. As the sole federal agency charged with fostering CAM-centered

partnership and collaborations, the Center exerts proactive leadership among key playersBfederal agencies, the scientific community, CAM practitioners, and academic institutions.